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THE DISTRIBUTION OF IODINE WITH SPECIAL REFERENCE TO GOITER

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I. EARLY HISTORY. Iodine was discovered by Courtois (1) in 1811 during the British blockade of France. Napoleon was cut off from Chilean saltpeter for the making of gunpowder, and Courtois had a nitrification plant in which the calcium nitrate was treated with the ash of seaweed to produce potassium nitrate. The nitrate oxidized the iodide in the ash of seaweed to iodine, which crystallized in the vats. He observed that it was soluble in ether and alcohol and combined with H_2 to form HI. He states that Pb and Ag iodides are insoluble. Gay-Lussac (2) described iodates. Davy (3) found iodine in the seaweed, Fucus. Fyfe (4) found it in sponges in 1815–19. Colin and deClaubry (5) showed that iodine on starch produced a blue color. Angelini (6) and Cantu (7) found iodine in a number of mineral springs that were reputed to cure goiter. Egidi (8) and Pleischl (9) found it in spring water. Boussingault (10) found it in spring water and in sea water of salt marshes, and Laurens (11) found it in Mediterranean water. Balard (12) found it in marine animals. Vauquelin (13) found it in various minerals. Müller (14) observed it in watercress. In 1820 the chemist, Dumas, collaborated with the physician Coindet (15) in a careful study of the use of iodine in the treatment of goiter. Iodine, after its discovery, had been considered a panacea, but gradually the relation of the curative properties of iodine to that of seaweed and burnt sponge, which were known to contain large amounts of iodine, was realized. This use of seaweeds and sponges was known to the ancients and recommended by Roger de Palermo in 1180. Coindet found that iodine would cure some cases of goiter. He dissolved 48 grams of iodine per ounce of alcohol and administered 10 drops, three times a day. At the end of one week, he doubled the doses and a few days later raised each dose to 50 drops (containing about one grain of iodine). Some goiters disap-

peared in six to ten weeks, others not at all. Coindet (16) gave warning against over-dosing or giving it to sick patients or those who cannot be seen by the physician daily. Later he applied it in a salve over the thyroid.

Preparations of the thyroid gland were used four thousand years ago by the Chinese, and the use of burnt sponge dates back to antiquity, but notwithstanding this knowledge, and the work of Coindet, goiter remained world-wide in distribution.

Lassaigne (17) observed that iodine in aqueous solution is adsorbed by charcoal and this observation may serve as a criticism of methods in which the material to be analyzed is charred. Davy (18) synthesized ICl, Gay-Lussac (19) ICl and ICl_3, and Balard (20) IBr. The formation of these substances may interfere with the determination of iodine if bromide and chloride are very abundant in the sample and an oxidizing agent is added.

De l'Orme (21) in 1836 and Stein (22) in 1840, found iodine in some samples of cod liver oil. Boussingault (23) found that at Cartago, in Cauca Valley, and at Sanson (2538 meters), in the Province of Antioquia, in the goitrous Andes, there was iodine in the salt used (salt from iodine-containing salt springs in Antiochia) and goiter was unknown, but at Mariquita and Santa Fe de Bogota (2640 meters), goiter was endemic. Goiter appeared at Cartago when the salt from the mineral spring of Galinde was replaced by the non-iodized salt of Zipaquira. The sea salt of Guaca was called a cure for goiter. One family at Antiochia purified their salt to improve its taste and developed goiter. He suggested that salt containing iodine be sold by the government.

In 1850, Chatin (24) started out systematically to study the distribution of iodine in France. Following Müller he found that iodine was not confined to watercress or even to the family of Cruciferae but was common to all aquatic plants. He states that plants in running water contain more iodine than those in stagnant waters because the plants extract it from the water. Chatin's method was to ash the plant (in some cases, after the addition of potash, to help hold back the iodine) boil the ashes in four times their weight of distilled water for fifteen minutes, filter and add starch and nitric acid. In 1852, Thenard, Gaudichaud and Bussy (25) pointed out that the CO_2 liberated by the acid might carry away a little iodine. Chloride also interfered with the determination. When using nitric acid some chlorine is formed. They advocate the extraction of the iodide from the dried leachings of the ash with alcohol and quantitative determinations. Meyrac

(26) found that certain water plants contain iodine that cannot be extracted from them by boiling in water for twenty-four hours. Personne (27) reported iodine in a water plant. Bussy (28) found iodine appearing during the distillation of coal (3700 cc. of the ammonia fraction of the distillate gave 0.59 gram iodine determined as palladous iodide). Mene (29) obtained the same result.

Chatin (30) extended his studies to fresh water plants of Asia, Africa and America, finding iodine in coal, in fresh water animals and rats. He found iodine in water, and said iodine is more abundant in ferruginous waters and waters from igneous rocks. He found waters from melting glaciers and snow deficient in iodine. He found iodine in the gangue of rock salt, in commercial potash, soda, ammonia and sea salt, and also in liquors and milk. He advanced the hypothesis that the deficiency of iodine in certain countries causes goiter. By changing the water, or by the use of wine, watercress, eggs or sea salt, goiter might be prevented.

Marchand (31) claimed that all natural waters contain iodine which is transported from the sea and brought down in rain, snow and hail. He agreed with Chatin that the deficiency of iodine was the cause of goiter and cretinism. Chatin (32) found that iodine evaporates from water, and more rapidly the higher the temperature. He drew air through potash bulbs and analyzed the potash solution for iodine. He found that 4,000 liters of air in Paris contained 0.002 mgm. iodine. A man breathes 8,000 liters of air a day which would mean 0.004 mgm. of iodine. He would get about the same amount of iodine in 2 liters of drinking water from the region of Paris. (We know now that much or all of this iodine in the air is contained in the dust which consists partly of dried organisms.) He found that air exhaled from the lungs retained only one-fifth of the iodine and supposed that the alkali of the blood absorbed the iodine. He found from 0.08 to 0.5 mgm. in 10 liters of rain water in Paris, but the iodine might show a diminution with time if the rain was long continued. He found more iodine in rain water than in any other fresh water, but it is possible that this may be due to the fact that in rain water the substances interfering with the determination were eliminated.

In 1851, Fourcault (33) studied the relation between goiter and cretinism, and iodine, in various places, and found goiter to be due to insufficiency of iodine in water and food. Chatin (34) studied France, Switzerland and Piedmont, and found little iodine in the water of the goitrous portions. The iodine in rain water of the same locality varied.

He found very little iodine in the goitrous regions of the Alps, particularly in the goitrous valleys.

Grange (35) introduced nitrous acid as a reagent for the oxidation of iodide to iodine. The starch iodide reaction could be used in solutions containing five parts per million of iodine. If solutions contained one part per million, or less, he used the method of Rabourdin (1850) by extracting iodine with chloroform. He confirmed some of Chatin's results.

In 1852, Chatin (36) analyzed the iodine that could be extracted from soil with boiling water. He said that food contains different amounts of iodine according to the soil in which it is grown. This applied to wheat, milk and cheese. He divided the region studied into six zones, but we will combine the third with the fourth, and the fifth with the sixth as he did in some of his papers. In the first zone or region of Paris, 8,000 liters of air, 2 liters of water, the average food taken by one person in 24 hours or the leachings of 10 grams of soil with boiling water, contained from 0.005 to 0.01 mgm. of iodine. In this region goiter and cretinism were unknown. In the second zone of the Soisonais, goiter is rare and cretinism unknown. Some of the waters are deficient in iodine. In the third zone of Lyon and Turin, goiter is frequent and some cretinism exists. In the same amounts of material is found 0.001 to 0.002 mgm. of iodine. In the fourth zone, the Alpine Valleys, goiter and cretinism are endemic. The same amounts of material contain only 0.0005 mgm. iodine. He advocated the use of rain water in the second zone, and the choosing of water from certain mineral springs and importing iodine-rich foods in the third zone. In the fourth zone he advocated the use of water from sulphur springs after the removal of the sulphur; also the use of iodized salt already advocated by Boussingault and Grange. He stated that the animal and vegetable products can be iodized by giving the animals mineral water to drink and irrigating the plants with mineral waters.

Chatin (37) found chlorides in the rain water near the sea and 5 mgm. of organic matter per liter (indicating the origin of iodine in the rain water from sea spray and dried organisms).

Chatin (38) studied iodine in different water supplies of Paris, London and Turin. In some of these in Paris, sewage was abundant and the chlorides from urine interfered with the determinations. He found that iodine in the sewage of Paris was greater than that in the Seine. He advised the people using well water around Paris to substitute rain water on account of its higher iodine content.

The Paris Academy appointed three commissions of which Thenard, Magendie, Dumas, Gaudichaud, de Beaumont, Pouillet, Regnault and Bussy, were members, to verify the observations of Chatin. They confirmed the chemical studies of Chatin, doing some of the experiments themselves and observing Chatin perform others, but did not accept his conclusions in regard to the cause of goiter. An extended report is given by Marchand, Niepce and Meyrac (39) in 1852, and another by the commission (40) in 1853.

In 1853 Chatin (41) studied two villages, Fully and Saillon, on the right bank of the Rhone. Goiter and cretinism were very prevalent in Fully, whereas Saillon had not had noticeable goiter until the water supply was changed. The source of the water supply had been from a spring that was rich in iodine, taken as it flowed into the River Salente. A change was made, drawing the water from the river at a point above the mouth of the spring, and goiter appeared in the population of Saillon.

Casaseca (42) found a small amount of iodine in the water of the River Almendares in Cuba, also in watercress from the river. He supposed that this amount of iodine was too small to account for the lack of goiter in Cuba. Chatin (43) disagreed with him, claiming that the iodine found was sufficient to prevent goiter.

Chatin's data were presented to the Academy in the form of tables which were not published but abstracts of his work appear elsewhere (44). In 1854 Macadam found iodine in a number of edible plants. In 1858 Rilliet and Boinet took part in a symposium on iodine and goiter before the Paris Academy of Medicine. The work of Chatin seemed fairly conclusive, but was accepted only by a very few persons. In 1867 Saint-Lager (45) stated that deficiency of iodine is not the cause of endemic goiter (page 239) and quoted Cantu as having found iodine in many waters of goitrous regions in Piedmont, Brunner as having found the same in so-called goiter springs in the canton of Berne, and Berbert in the goitrous water of St. Pancrace in Savoy, and quoted Casaseca. He stated that Dejean, Germain and Moretin did not find any more iodine in the waters of the Jura that supply populations in which goiter is not endemic than in the water in endemic localities. Poulet did not find iodine in the water of Belfahy where there is no goiter. The Lombardy Commission did not find iodine in many high valleys in Lombardy where cretinism is unknown.

A number of chemists discussed sources of error in the method, as, for instance, iodine in the reagents. The reader is referred to the objections of Nadlar (46) in 1861, although we believe his criticisms

unfounded. Chatin (47) reviewed his methods in 1876 and advocated dividing the sample and using several methods.

II. Iodine in the thyroid. During the period from 1873 to 1895 Pasteur emphasized to the medical profession the germ theory of disease. So convincing were Pasteur's arguments that the older chemical theories were neglected. The germ theory was expected to explain everything and the medical profession hoped for the discovery of a germ causing goiter. In 1895, the year of Pasteur's death, Baumann (48) discovered iodine in the thyroid gland. The year before, Emminghaus and Reinhold (49) had shown that the administration of thyroid caused rapid reduction of goiter. Sheep's thyroid (as soup) had been used medicinally by the Chinese five thousand years before Christ but its effects have up to this time apparently not been recorded. Baumann worked in collaboration with the Bayer aniline dye corporation. The thyroids of one thousand sheep were used in the production of a substance known as thyroiodine (iodothyrin) which seemed to have the same physiological effects as thyroid. After twice dissolving and reprecipitating it, Baumann found it to contain 9.3 per cent iodine. He obtained tests for iodine in a colloid goiter and other thyroid glands.

Murray (50) in 1891 had a myxedematous patient who had been sick for five years, and the symptoms were relieved by hypodermic injections of thyroid extract. He found the extract just as effective taken by mouth, and on this treatment the patient lived in good health twenty-eight years and died at the age of seventy-four after taking the extract of the thyroids from 870 sheep. It has been shown that not only is the gland reduced in size by the natural production of the active principle, but also taking the active principle by mouth is a substitute for the secretion of the gland in the body.

Kendall (51) in 1914 isolated thyroxin. He finally obtained enough for elementary analysis and gave it the formula $C_{11}H_{10}O_3NI_3$. It is not the purpose of this paper to go into the chemistry of thyroxin but merely to state that it contains 65 per cent of iodin. Harrington (52) in 1926 made some further advances in the study of the chemical structure of thyroxin giving it the formula $C_{15}H_{11}O_4NI_4$. It is claimed that thyroxin has the same physiological effect as thyroid extract, but after its administration, the full effect does not appear until about seven days, so there is much yet to be investigated in regard to its behavior in the body.

Baumann continued his work on iodine in the thyroid and this work was taken up by a large number of workers. It is not possible here to review all this literature, but "iodine has been found in the thyroids of

five species of elasmobranch and one of holocephaloid fishes, one amphibian, two reptilians, six species of birds and fourteen species of mammals" (Cameron, 53). The average iodine content of the dry thyroid has been reported as 0.06 to 0.75 per cent. The average number of milligrams in the whole human thyroid has been reported from 4 to 16. Zunz (54) in 1919 determined the iodine content of the thyroids of normal men killed in the war. He found the whole gland to contain from 3 to 45 mgm., the average being 16 mgm. On the dry basis there was 0.04 to 0.4 per cent, and on the wet basis there was 0.01 to 0.1 per cent iodine. Kendall (55), on the basis of the iodine content of the thyroid of normal persons in a goitrous region, has accepted the value of 10 mgm. of iodine in the total thyroid in the normal human adult. This holds true also of Japanese, according to Fukushima (56). It seems evident that the thyroid can get along with only 10 mgm. of iodine without showing symptoms of goiter. It is claimed by Tatum (57) and Van Dyke (58) that in the thyroid gland most of the iodine is in the colloid and very little in the cells. The iodine content increases at least up to about the age of fifty.

The iodine content of the thyroid may be increased by feeding iodine. Simpson and Hunter (59) found the iodine content of sheep's thyroid to be 0.53 per cent of the dried tissue. By feeding iodine for six weeks it was raised to 1.15 per cent. Occasionally a patient has taken large doses of potassium iodide and then died, and on analysis of the thyroid it was shown to contain up to 380 mgm. (60) or even higher.

Attempts to show that the normal thyroid contains more iodine than the thyroid in cases of simple goiter have led to varying results which may be interpreted, however, by assuming that goiter is primarily a hypertrophy of the gland due to deficient thyroxin in the body, since feeding thyroid prevents hypertrophy or growth of the gland (61). The deficiency of thyroxin at first leads to a rapid proliferation of the cells of the thyroid with low average iodine content (0.035 per cent of dry substance) (62). If the enlarged gland is able to obtain enough iodine to produce sufficient thyroxin it goes into a colloid stage with an average of 0.35 per cent iodine on dry basis. In the colloid stage no symptoms of hypothyroidism, or very slight symptoms, are manifested. The fact that sufficient thyroxin is produced shows that iodine has been obtained. We should then not expect to find a decreased amount of iodine in a colloid goiter. Owing to the increase in size of the gland, there may be, on the contrary, an increased amount of iodine in it. It has been usually found, however, that in cases of goiter the iodine per gram of dried tissue is less than in a normal condition.

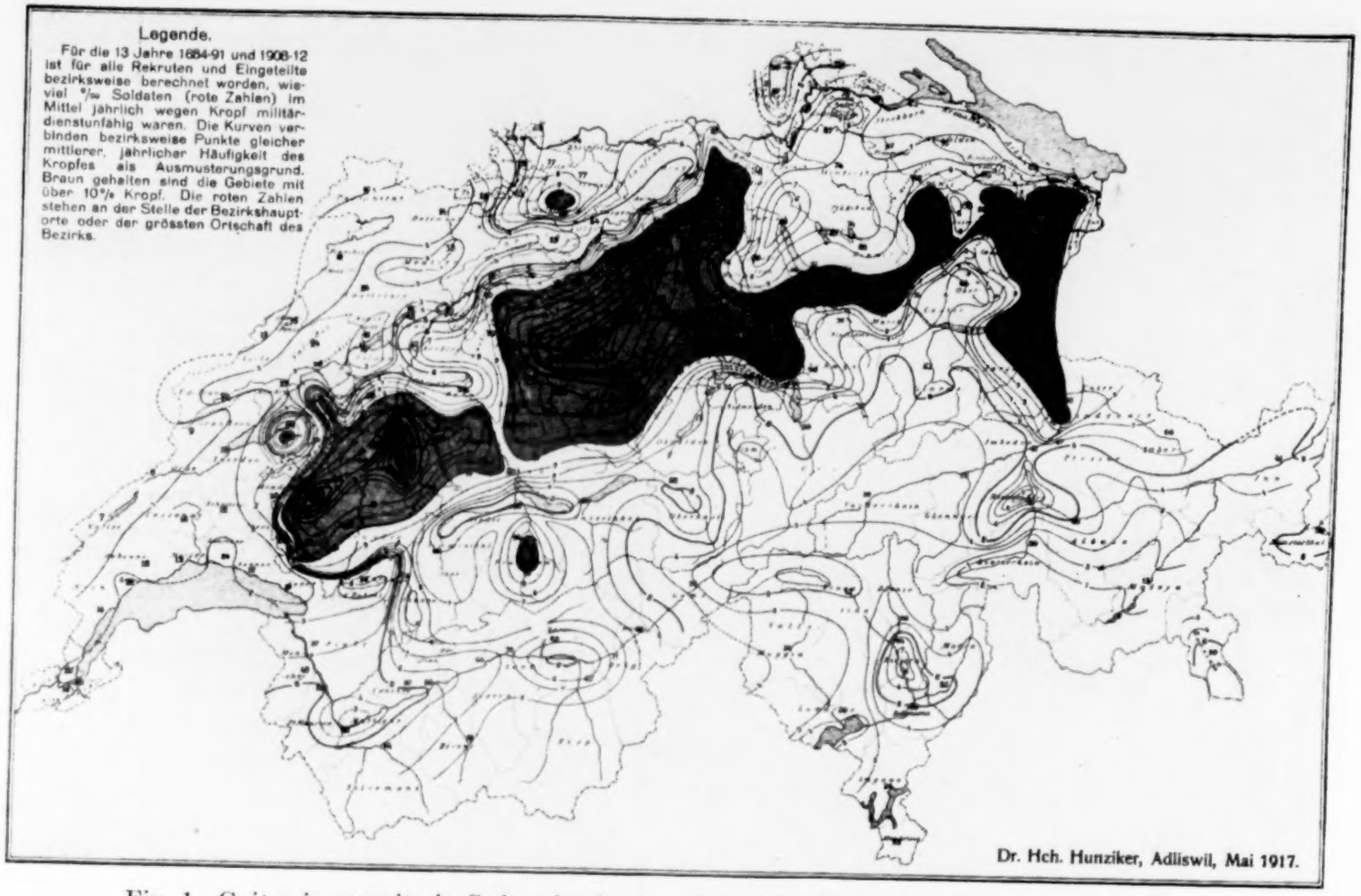
Legende.
Für die 13 Jahre 1884-91 und 1908-12 ist für alle Rekruten und Eingeteilte bezirksweise berechnet worden, wieviel ‰ Soldaten (rote Zahlen) im Mittel jährlich wegen Kropf militärdienstunfähig waren. Die Kurven verbinden bezirksweise Punkte gleicher mittlerer, jährlicher Häufigkeit des Kropfes als Ausmusterungsgrund. Braun gehalten sind die Gebiete mit über 10% Kropf. Die roten Zahlen stehen an der Stelle der Bezirkshauptorte oder der grössten Ortschaft des Bezirks.
Dr. Hch. Hunziker, Adliswil, Mai 1917.

Fig. 1. Goiter in recruits in Switzerland, after Hunziker, Corr. Bl. f. Schw. Aerzte, 1918

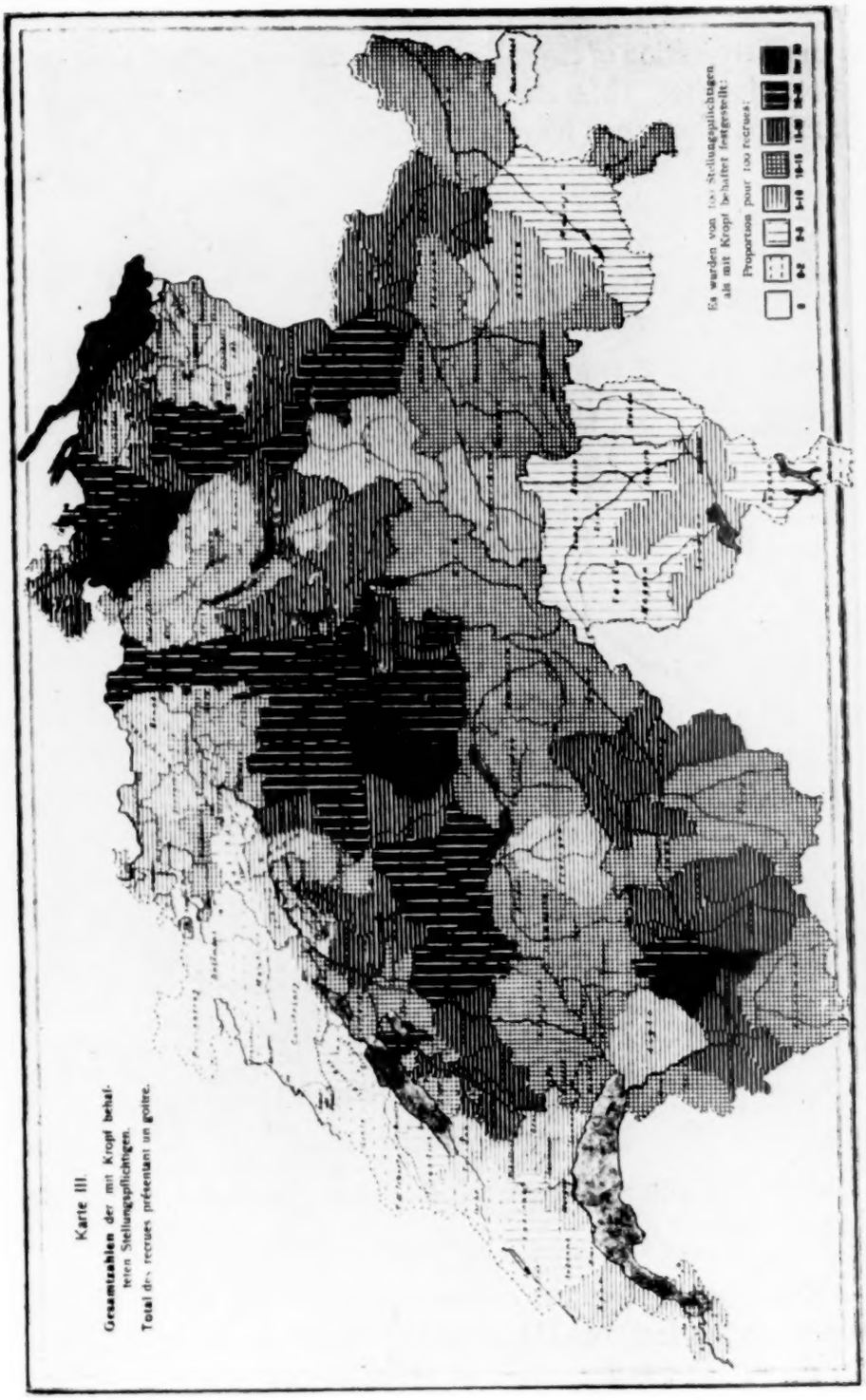
Karte III.
Gesamtzahlen der mit Kropf behafteten Stellungspflichtigen.
Total des recrues présentant un goitre.
Es werden von der Stellungspflichtigen als mit Kropf behaftet festgestellt:
Proportion pour 100 recrues:

Fig. 2. Goiter in recruits in Switzerland, after Stiner, Schweiz. Med. Wochenschr., 1924

III. Distribution of goiter. Owing to the fact that no very extensive iodine analyses of thyroids have been made, the best data we have on the distribution of thyroids of low iodine content are data on the distribution of goiter. Marine and his co-workers showed that if the dry thyroid contains much less than 0.1 per cent of iodine, it is hyper-

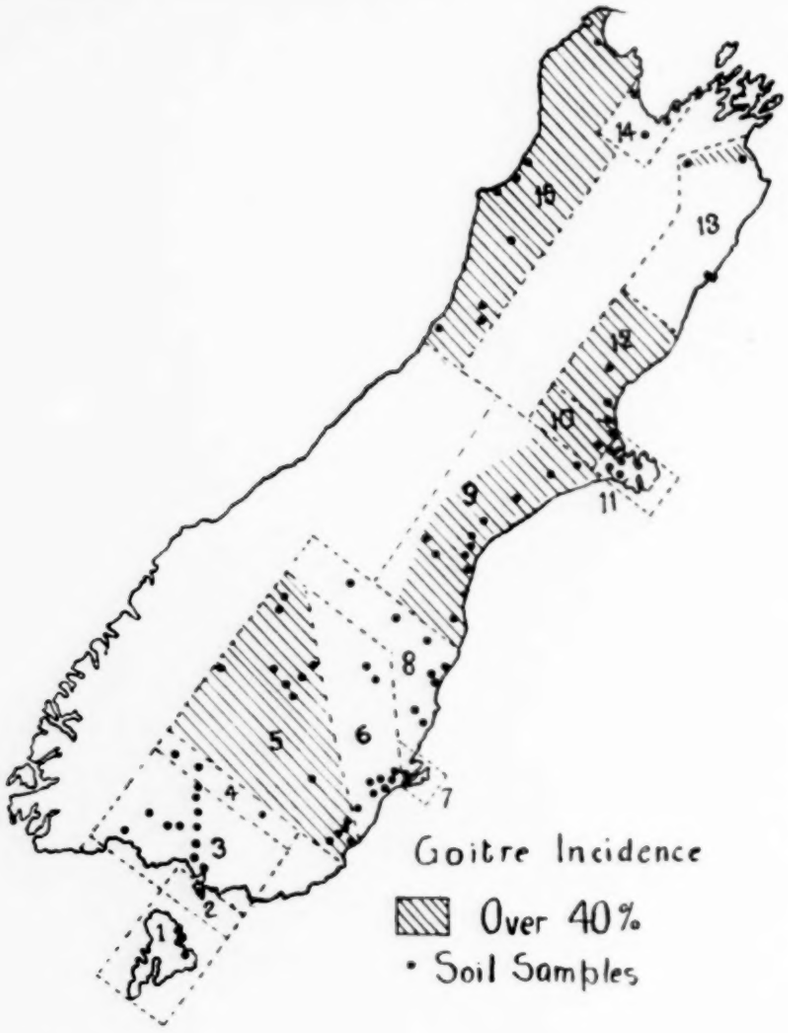

Fig. 3. Districts of goiter-incidence and localities of analyzed soils in New Zealand, South Island.

plastic. Although colloid goiters contain more than 0.1 per cent iodine, they were once hyperplastic and then contained less; so the total number of goiters shows the total number of thyroids that contain, or once contained, less than 0.1 per cent of iodine.

The earliest general work on the distribution of goiter is that of

Hirsch (63). The only countries in the world which were free from goiter, according to Hirsch, were Norway, Denmark and New Zealand. Goiter and cretinism have been found in Norway and Denmark. New Zealand has been shown to be a goitrous country (64). According to

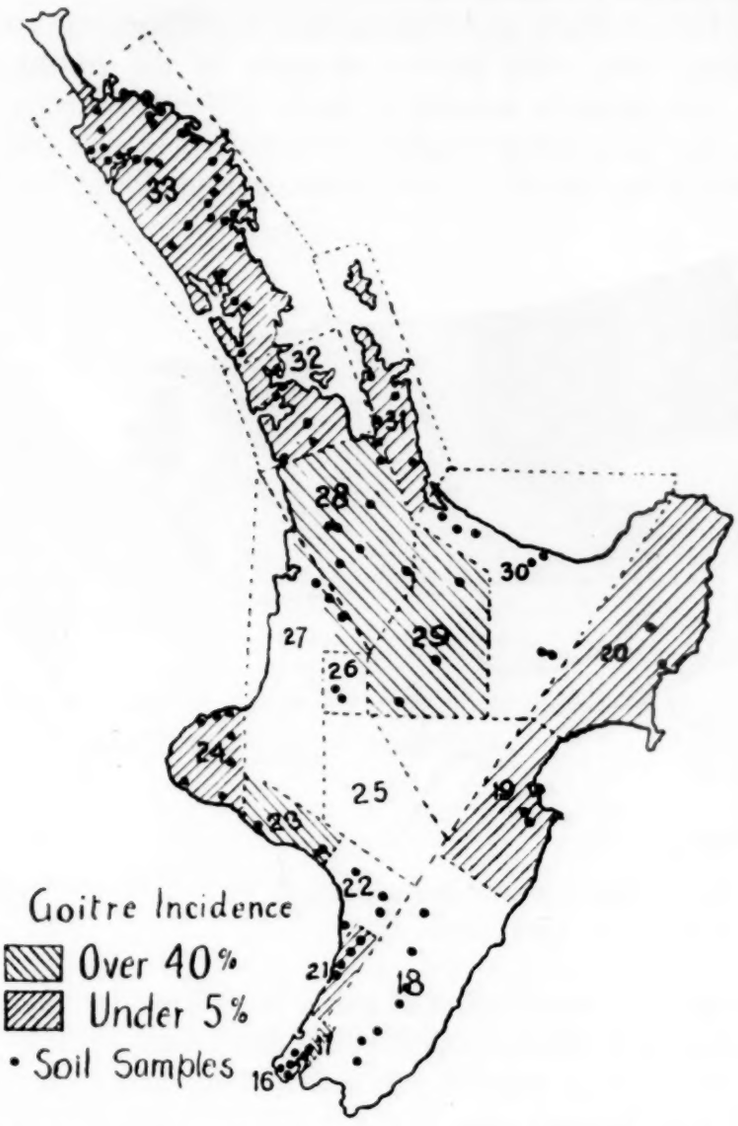

Fig. 4. Districts of goiter-incidence and localities of analyzed soils in New Zealand, North Island.

Hirsch, goiter had decreased in older settled communities, but increased after the first settlement of America, and then decreased. In families in which goiters have been present for many generations, cretinism may develop if the iodine deficiency is intense. About eighty years ago there

were estimated twenty-eight cretins per thousand population in the district of Aosta, Italy; about fifty years ago there were estimated twenty-three cretins per thousand population in the valley of the Maurienne in France, and nine per thousand in Uri, Switzerland. Cretinism is disappearing from these regions.

In the United States and Canada there have been reported 340 cases of cretinism (65). The parents of many of the cretins came from Europe. Cretinism is endemic in parts of South America (66). Not only are the early settled regions of Canada goitrous, but so are the newer settled regions (67). Mexico has considerable goiter (68).

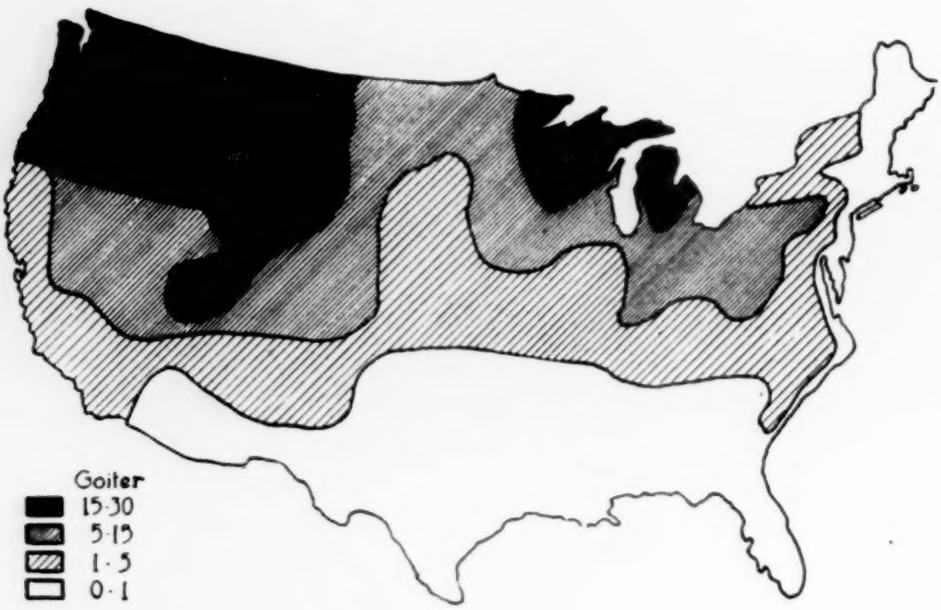

Fig. 5. Goiter rate per 1000 drafted men in U. S. A., after McClendon and Williams, Jour. Amer. Med. Assn., 1923.

The geographic distribution of goiter is so irregular that large scale maps are necessary to show the details. Such maps have been prepared only for Switzerland (figs. 1 (69) and 2 (70)), and to a less detailed extent of New Zealand (figs. 3 and 4 (64)). By omitting details and smoothing out local irregularities, a small scale map of the United States has been prepared (fig. 5 (71)).

To show the difference in sex and age, college girls of almost the same age (slightly younger) as the boys examined in the first draft (fig. 5) were examined in some state universities. At the University of Illinois 45 per cent of the girls had goiter (72), Indiana 33 per cent (73) and

Wisconsin 37 per cent (74). These figures are more than ten times as great as those shown in figure 5 but small goiters were overlooked by the Draft Board.

Goiter is most common in girls about the age of puberty as shown by comparison of the following examinations of school girls with the preceding figures:

	Per cent goitrous
Michigan (75):	
Houghton County	71
Wexford County	56
Midland County	33
Malcolm County	26
Grand Rapids—Kent County	40
Minnesota (76):	
St. Paul	73
Average of 13 towns	71
Montana (77):	
Fergus County	49
Carbon	39
Cascade	34
Big Horn	25
Hill	13
Ohio—Cincinnati	40
Colorado (78)	40
Utah (79)	54
Kansas (80)—Topeka	50
Connecticut—Average	29
Manitoba (81)	43–79

These figures may be compared with those of girls in Holland according to the Utrecht Goiter Commission 1924:

City	*Per cent goitrous*
Breda	94
Utrecht	49
Leeuworden	49
Middelburg	22

IV. Iodine in rocks and minerals. Gautier (82) determined the iodine content of a number of rocks as follows:

Rock	*Iodine, parts per billion*	*Rock*	*Iodine, parts per billion*
Granite	1,250	Apatite (Cl & F)	230
Mica	780	Apatite	0
Granite	230	Ophite	0
Granulite (contains apatite)	170		

Von Fellenberg (83) made more extensive analysis as follows:

Rock	*Iodine, parts per billion*
Granite	440
Porphyritic	380
Gneiss-granite	810
Pumice	250
Cristalline-shale Gneiss	380
Protogene	440
Aplite	400
Pegmatite	350
Sericite-quartz-shale	220
Amphabolite	250
Serpentine	380
Shale (Strahlsternschiefer)	190
Chlorite	200
Hornblende-shale	350
Biotite-mica	330
Sedimentary rock	
Anhydrite	300
Gypsum	250
Gypsum	270
Quartzite	1,100
Quartzite	3,700
Quartzite	8,850
Calcite	230
Limestone	440
Dolomite	320
Diluvium	
Pebbles and Sand from last ice age	970
Pebbles and Sand from last ice age (yellow loam)	1,040
Pebbles and Sand from last ice age (fine sand)	1,380
Pebbles and Sand from last ice age (fine sand)	1,090

Tertiary	*Iodine, parts per billion*
Molas (marine)	700
Molas (marine)	1,600
Molas (marine)	2,300
Molas (marine)	1,500
Molas (marine)	1,510
Molas (fresh water)	230
Flysch	240
Flysch	230
Flysch-schale	200
Nummulitic limestone	750
Chalk	
Marine Chalk (Seewerkalk)	250
Wangschichten	170
Neocomium	310
Neocomium-shale	780
Jura	
Malm	500
Malm	700
Malm	1,760
Malm	5,400
Malm (containing fossil)	9,200
Dogger	830
Lias	320
Bündner-shale	380
Trias	
Red Dolomite	1,000
Upper Dolomite	420
Gypsum	250
Anhydrite	300
Keuper (Grindstone)	850
Limestone (Muschelkalk)	430

He found that the presence of fossils greatly increased the iodine content of a piece of sedimentary rock. It is well known that coal is rich in iodine. Since he supposed that iodine might be distributed with other halogens he analyzed a number of halogen bearing minerals as follows, in comparison with non-halogen bearing minerals:

Halogen-bearing minerals	*Iodine, parts per billion*
Borocite ($Mg_7B_{16}O_{30}Cl_{12}$)	440
Apatite, $Cl(F)Ca_5(PO_4)_3$	300
Apatite	440
Pyromorphite, $ClPb_5(PO_4)_3$	10,000
Pyromorphite	400

	Iodine, parts per billion
Topaz	540
Topaz	380
Turmaline	650
Turmaline	400
Turmaline	130
Vesuvianite, $OH(F)Ca_6Al_3Si_5O_{21}$	1,130

	Iodine, parts per billion
Vesuvianite	1,250
Scapolite, $Na_4Al_3Si_9O_{24}ClCa_4$-$Al_6Si_6O_{25}$	2,200
Other minerals	
Rock Crystal, SiO_2	200
Smokey Topaz	500
Amethyst	420
Flint nodules	630
Calcite, $CaCO_3$	50
Gypsum, $CaSO_42H_2O$	270
Earths	
Hematite, Fe_2O_3	440
Limonite, $Fe_2O_33H_2O$	750
Pyrite	200
Copper	670
Copper	4,000
Cuprite, Cu_2O	38,000
Cuprite, Cu_2O	38,800
Bornite, Cu_3FeS_3	310
Proustite, Ag_3AsS_3	550
Zincblende, ZnS	950
Casseterite, SnO_2	70
Cinnabar, HgS	500
Cerussite, $PbCO_3$	0
Galena, PbS	120
Wulfenite, $PbMoO_4$	8,558
Wolframite $(FeMn)Wo_4$	550
Pitchblende $(UPb_2)_2U_2O_{12}$	940

Von Fellenberg and Lunde (84) made more careful studies, particularly in regard to handling the samples. The samples were broken out of the centers of large masses of rock in order to avoid any contamination. The method was also carefully scrutinized. The results are as follows:

Rock	*Iodine, parts per billion*
Granite	200
Larvicite	300
Labradorite	230
Obsidian	320
Basalt	310
Minerals	
Marble	550
Marble	70
Titanite	770
Hypersthene	940
Labradorite	440
Biotite	500
Hornblende	160
Scapolite	230
Sodalite	900
Phlogopite	630
Aplite	180
Perithitic-microcline	370
Albite	150
Muscovite	690
Fluorspar	550
Smoky Quartz	330

In conclusion we may observe that iodine is widely distributed in rocks and minerals of all kinds. The figures given are probably low rather than high since there is liability of loss of iodine in dissolving the rocks, particularly the silicates. Von Fellenberg and Lunde were not able to recover all the iodine added in order to test the method. On the anatomic disintegration theory of the origin of the elements, the elements of even atomic weight are most abundant because most of them have arisen by extrusion of a helium nucleus out of the atom. The elements of odd atomic weight are rare, and iodine comes in this class. It is probably distributed now largely where it originated. There has not been a sufficient amount of it to be easily concentrated by geological forces.

V. IODINE CONTENT OF SOILS. Von Fellenberg compared the iodine content of rocks with that of soils which arose from weathering of the same rocks, as follows:

	Iodine, parts per billion		*Iodine, parts per billion*
Gneiss	380	Malm	180
Soil from Gneiss	1,320	Soil from same	6,400
Amphabolite	380	Malm	1,760
Soil from Amphabolite	3,150	Soil from same	5,950
Sand and gravel from last ice age	970	Bündners-shale	380
Soil from the same	1,570	Soil from same	1,000
Flych	240	Red Dolomite	1,000
Soil from same	1,700	Soil from same	2,200

He concludes that the soil receives iodine from water that percolates through it, and performed some experiments of leaching potassium iodine solution through earth to determine the increase in iodine content. He supposes that the increased iodine content of the soils comes from rain water.

Von Fellenberg (85) determined the iodine content of soils in various localities of Switzerland as follows:

	Per cent goitrous	*Iodine, parts per billion*
Effingen	1 0	11,900
Hornussen	12 1	4,940
Hunzenschwil	56 2	620
Kaisten	61.6	1,400

The most extensive survey of the iodine content of soils was made in New Zealand by Hercus, Benson and Carter (64).

Iodine in New Zealand soils

Locality	*Geology*	*Iodine, parts per billion*
South Island:		
Stewart Island:		
Half Moon Bay	Granite	13,400
Horse Shoe Bay	Granite	12,000
South of Paterson Inlet	Mica schist	600
Bluff:		
Partly weathered	Norite	400
Well weathered	Norite	4,200
Virgin bush	Norite	1,400
Invercargill and Southland Plain:		
Invercargill—South	Silt	400
Invercargill—South	Silt	2,000
Invercargill—Georgetown	Silt	400
Invercargill—Gardens	Silt	800
Invercargill—Waihopai	Silt	2,200
Invercargill—North	Silt	10,60
Royal Bush—Gardens	Silt	5,800

Locality	*Geology*	*Iodine, parts per billion*
Invercargill and Southland Plain:		
Royal Bush—Lea	Silt	5,000
Royal Bush—Virgin	Silt	600
Royal Bush—Paddock	Silt	1,600
Royal Bush—in ditch	Swamp	200
Royal Bush—in Creek Bed	Swamp	400
Taramoa—School	Silt	1,600
Taramoa—Millars	Silt	5,000
Taramoa—Burns	Silt	5,000
Taramoa—Virgin	Silt	9,600
Tuatapere	Silt	0
Tuatapere	Silt	0
Orawia	River sand	200
Otautau	Silt	200
Otautau	Silt	1,600
Otautau	Silt	1,000
Drummond	Silt	2,400
Drummond	Silt	800
Winton—Gap Road	Silt	600
Winton—North	Silt	600
Centre Bush—Hill	Silt	1,000
Centre Bush—Hill	Silt	1,000
South Dipton	Silt	600
Dipton	Silt	400
Caroline River Flat	Silt	400
Waimea Plains:		
Mossburn	Silt	1,200
Castle Rock	Silt	1,000
Gore (Avon Street)	Silt	200
Gore (Avon Street)	Silt	200
Gore (Kitchener Street)	Silt	200
Gore (Kitchener Street)	Silt	600
Clutha Valley:		
Kaitangata—Efi Street	River sand	1,000
Kaitangata—Pool Street	River sand	1,500
Kaitangata—School	River sand	400
Kaitangata—No. 1 Mine	River sand	400
Kaitangata—No. 1 Mine	River sand	1,000
Kaitangata—Water Street	Silt	300
Kaitangata—Berry Street	Silt	200
Kaitangata—River Bank	Silt	400
Kaitangata—River Bank	Silt	200
Lovell's Flat	Silt	400
Stirling	River sand	200
Stirling	River sand	300
Stirling	River sand	400
Matau	Mica schist	200
Matau	Mica schist	100
Inch Clutha	Silt	400
North Clutha	Paleo-mesozoic	1,000
North Clutha	Paleo-mesozoic	900
Balclutha—Flat	Silt	500
Balclutha—Subsoil Flat	Mica schist	1,000
Balclutha—Subsoil Flat	Mica schist	0
Balclutha—Renfrew Street	Mica schist	0
Balclutha—Argyle Street	Mica schist	200
Balclutha—Clyde Street	Mica schist	200
Balclutha—School	Silt	200

Locality	*Geology*	*Iodine, parts per billion*
Clutha Valley:		
Balclutha—Pumping Station	Silt	600
Balclutha—Sinclair's	Silt	700
Balclutha—Kelsy's	Silt	700
Balclutha—O'Hara's	Silt	1,000
Balclutha—Nash's	Silt	0
Balclutha—Rosebank	Silt	1,000
Balclutha—Rosebank	Silt	1,000
Beaumont—Hill	Mica schist	1,000
Beaumont—Hill	Mica schist	200
Beaumont—Hill	Mica schist	400
Alexandra (a)	Silt	0
Alexandra (b)	Silt	200
Alexandra (c)	Silt	200
Alexandra (d)	Silt	200
Alexandra (e)	Silt	200
Alexandra (f)	Silt	200
Alexandra (g)	Silt	400
Alexandra (h)	Silt	400
Alexandra (i)	Silt	700
Alexandra (j)	Silt	2,400
Clyde—Hill	Mica schist	400
Clyde—Flat	Silt	200
Clyde—Flat	Silt	400
Cromwell (a)	Silt	400
Cromwell (b)	Silt	200
Cromwell (c)	Silt	0
Cromwell (d)	Silt	0
Cromwell (e)	Silt	0
Cromwell (f)	Silt	0
Cromwell (g)	Silt	0
Cromwell (h)	Silt	200
Cromwell (i)	Silt	200
Chatto Creek	Mica schist	0
Manuherika Valley	Silt	0
Queenstown	Mica schist	0
Lake Hawea	Mica schist	200
Lake Hawea	Mica schist	200
Lake Hawea—"Timaru Creek"	Mica schist	200
Taieri Valley and Milton:		
Naseby	Silt	600
Kokonga	Basalt	200
Kokonga	Basalt	800
Silverstream—Gorge	Mica schist	700
Silverstream	Silt	700
Silverstream—Butter Factory	Silt	200
Mosgiel	Silt	600
Mosgiel	Silt	700
Mosgiel (1 mile south)	Silt	1,600
Mosgiel (1 mile south)	Silt	1,400
Riccarton	Silt	200
Allanton	River sand	1,400
Taieri—Outram Road	Silt	500
Outram river bank	Silt	200
Outram river bank	Silt	600
Outram river bank	Silt	400
Maungatua	Silt	600
Berwick	Silt	400

Locality	*Geology*	*Iodine, parts per billion*
Taieri Valley and Milton:		
Berwick—Henley Road	Silt	200
Henley river bank	Silt	400
Henley Hill	River sand	0
Milton	Silt	1,000
Milton	Silt	800
Milton	Silt	800
Dunedin District:		
Water Race—South Road	Andesite	1,400
Dunedin—N.E. valley	Basalt	1,200
Dunedin—N.E. valley	Silt	1,400
Dunedin—N.E. valley	Basalt	1,200
Dunedin—N.E. valley	Basalt	1,600
Dunedin—N.E. valley	Basalt	1,600
Dunedin—Opoho	Basalt	2,000
Dunedin—Opoho	Andesite	1,200
Dunedin—Gardens	Basalt	1,500
Dunedin—Dalmore	Andesite	2,200
Dunedin—Woodhaugh	Silt	1,800
Dunedin—Forth Street	Phonolite	1,600
Dunedin—St. Margaret's	Andesite	2,200
Dunedin—Balmacewen	Basalt	2,500
Dunedin—Maori Hill	Andesite	1,200
Dunedin—Town Belt	Andesite	1,000
Dunedin—Dunottar	Andesite	1,200
Dunedin—Roslyn	Andesite	1,000
Dunedin—Roslyn	Basalt	1,800
Dunedin—Kaikorai	Basalt	1,400
Dunedin—Belleknowes	Basalt	3,300
Dunedin—Belleknowes	Basalt	3,000
Dunedin—Jubilee Park	Basalt	3,600
Dunedin—Mornington North	Basalt	1,400
Dunedin—Mornington South	Basalt	1,500
Dunedin—Carlton Hill	Basalt	3,000
Dunedin—Glen Road	Basalt	1,600
Dunedin—Lower	Clay	1,000
Dunedin—Monticello	Basalt	3,000
Dunedin—Rockyside	Clay	800
Dunedin—Industrial School	Clay	1,400
Dunedin—Main South Road	Clay	1,400
Dunedin—Kew House	Clay	2,600
Dunedin—St. Clair Hill	Basalt	1,700
Dunedin—George and Howe Street	Clay	1,400
Dunedin—George and Albany Street	Clay	1,100
Dunedin—Castle Street	Clay	2,000
Dunedin—Triangle	Swamp	4,000
Dunedin—Kensington	Swamp	5,600
Dunedin—South Dunedin	Swamp	3,000
Dunedin—Convalescent Home	Swamp	2,600
Dunedin—Forbury, Chinese Gardens	Swamp	1,500
Dunedin—Forbury, Chinese Gardens	Swamp	3,600
Dunedin—Coughtrey Street	Swamp	3,200
Dunedin—Richardson Street	Swamp	18,000
Dunedin—Princes Street, St. K	Swamp	15,000
Dunedin—Orphanage, St. K	Swamp	13,600
Dunedin—Orphanage, St. K	Swamp	18,200
Dunedin—Forbury Park	Swamp	2,400
Dunedin—Bay View Road	Swamp	3,600

Locality	*Geology*	*Iodine, parts per billion*
Dunedin District:		
Dunedin—Tahuna Park	Swamp	3,800
Dunedin—Tainui, Chinese Gardens	Swamp	6,400
Dunedin—Tainui, Chinese Gardens	Swamp	7,400
Dunedin—Botha Street	Swamp	6,400
Dunedin—Musselburgh Rise	Phonolite	3,400
Dunedin—Anderson's Bay Tunnel	Swamp	0
Dunedin—Anderson's Bay Tunnel	Swamp	0
Dunedin—Anderson's Bay Cemetery	Dune sand	200
Dunedin—Anderson's Bay Convent	Andesite	800
Dunedin—Anderson's Bay Glendining Home	Andesite	2,400
Dunedin—Highcliff Road	Basalt	3,600
North Otago District:		
Palmerston South—Flat	Silt	1,000
Palmerston South—Flat	Silt	400
Palmerston South—Hill	Greensand	800
Dunback	Silt	400
Dunback	Silt	700
Kahanui	Limestone	1,400
Maheno	Limestone	1,000
Oamaru—Wharfe Street	Limestone	1,000
Oamaru—Towey Street	Limestone	400
Oamaru—Chelmer Street	Basalt	3,400
Oamaru—Eden Street Hill	Basalt	2,400
Oamaru—Eden Street Flat	Gravel	700
Oamaru—Usk Street	Gravel	1,000
Oamaru—Trent Street	Gravel	1,000
Oamaru—Todd Street	Gravel	1,400
Oamaru—Davidson's	Gravel	200
Duntroon—Flat	Silt	400
Duntroon—Flat	Silt	500
Duntroon—Hill	Silt	1,000
Duntroon—Swakino Creek	Marl	0
Duntroon—Swakino Creek	Marl	0
Kurow—Swakino Creek	Marl	5,000
Kurow	Marl	4,500
Kurow	Marl	2,400
Kurow	Marl	2,500
Omarama	Paleo-mesozoic	200
Omarama	Silt	600
South Canterbury:		
Waimate	Silt	100
Te Ngawai		500
Mona Vale		200
Albury	Silt	600
Cave	Silt	400
Gleniti	Silt	100
Timaru (1 mile station)	Limestone	400
Timaru (2 miles W.)	Limestone	400
Timaru (3 miles N.W.)	Silt	400
Arowhenua	Silt	200
Temuka	Silt	400
Winchester	Silt	400
Rangitata Bridge	Silt	200
Ashburton	Silt	400
Rakaia	Gravel	0
Ladbrook	Silt	300

Locality	*Geology*	*Iodine, parts per billion*
Christchurch:		
Christchurch (a)	Silt	100
Christchurch (b)	Silt	1,200
Christchurch (c)	Silt	1,500
Christchurch (d)	Silt	1,100
Christchurch (e)	Silt	1,500
Christchurch (f)	Silt	1,000
Christchurch (g)	Silt	600
Christchurch (h)	Silt	500
Christchurch (i)	Silt	1,400
Christchurch (j)	River sand	0
Christchurch (k)	Silt	1,300
Christchurch (l)	River sand	200
Christchurch (m)	Silt	1,600
Christchurch—St. Martins	Silt	1,700
Christchurch—Spreydon	Silt	600
Christchurch—Papanui	Silt	1,000
Christchurch—Woolston	Silt	1,200
Christchurch—Sumner	Silt	700
Christchurch—St. Brighton	Dune sand	0
Banks Peninsula:		
Heathcote		1,500
Lyttleton	Basalt	900
Barry's Bay	Basalt	400
Pigeon Bay (a)	Basalt	600
Pigeon Bay (b)	Basalt	1,000
Pigeon Bay (c)	Basalt	1,000
Little River	Basalt	600
Birdling's Flat	Basalt	1,000
North Canterbury:		
Kaiapoi	Silt	500
Rangiora	Silt	600
Waikari	Silt	600
Marlborough:		
Kaikoura	Swamp	200
Kaikoura	Limestone	0
Blenheim	Silt	400
Wairau	Silt	600
Nelson:		
Nelson	Gravel	1,000
Nelson	Paleo-mesozoic	400
Nelson	Marl	3,800
Nelson (7½ miles N.E.)	Basalt	3,800
Nelson (14 miles S.)	Paleo-mesozoic	1,800
Richmond	Greensand	2,000
Stoke	Greensand	600
Stoke	Greensand	400
Wakefield	Gravel	1,000
Moutere Hills	Greensand	1,200
Motueka	Swamp	4,200
Motueka	Granite	400
West Coast:		
Collingwood	Gravel	200
Ngakawai	Gravel	400
Granity	Gravel	300
Westport	Gravel	400
Reefton	Silt	3,800
Moana	Silt	700
Kumara	Silt	4,800
Hokitika	Silt	400
Hokitika	Silt	200

Locality	*Geology*	*Iodine, parts per billion*
North Island:		
Wellington District:		
Wellington—Government Gardens	Paleo-mesozoic	600
Wellington—Mount Victoria	Paleo-mesozoic	800
Wellington—Island Bay	Paleo-mesozoic	6,200
Wellington—Miramar	Swamp	2,400
Wellington—Karori	Swamp	13,200
Makara (R. 757)	Paleo-mesozoic	600
Makara (R. 760)	Paleo-mesozoic	1,000
Makara (R. 763)	Paleo-mesozoic	3,800
Makara (R. 765)	Paleo-mesozoic	8,200
Oharui (R. 814)	Paleo-mesozoic	8,000
Oharui (R. 816)	Post-tertiary	400
Oharui (R. 818)		4,200
Oharui (R. 820)	Silt	2,600
Hutt Valley:		
Lower Hutt	Silt	1,200
Epuni	Silt	2,000
Wairarapa and Dannevirke:		
Martinborough	Silt	1,000
Greytown	Silt	400
Masterton	Silt	600
Ekatahuna	Tertiary	4,600
Ekatahuna (2 miles from)	Marl	400
Pahiatua	Silt	800
Woodville	Silt	8,600
Dannevirke	River sand	2,600
Dannevirke	River sand	2,400
Hawke's Bay:		
Hastings (5 miles E.)	River sand	600
Hastings (4 miles E.)	Silt	400
Hastings	Silt	400
Napier—Hospital Hill	Marl	1,200
Napier—Bluff Hill	Limestone	1,600
Gisborne District:		
Gisborne	Silt	1,600
Gisborne	Silt	2,000
Waikohu	Marl	200
Horowhenua Plain:		
Levin—South	Silt	16,600
Levin—East	Silt	7,800
Levin—Government Farm	Silt	12,800
Levin—Government Farm	Silt	13,000
Levin—North-East	Silt	14,600
Levin—North-East	Silt	15,800
Levin—North-East	Silt	18,200
Shannon	Silt	11,000
Palmerston District:		
Foston	Silt	600
Palmerston—North	Silt	1,000
Feilding	Silt	1,000
Feilding	Silt	1,000
Feilding	Silt	800
Marton	Silt	1,000
Wanganui and Patea:		
Wanganui—Keith Street	Silt	600
Wanganui—Keith Street	Silt	800
Wanganui—Bates Street	Silt	400
Wanganui—Pitt Street	Silt	1,000

Locality	*Geology*	*Iodine, parts per billion*
Wanganui Patea:		
Wanganui—Nelson Street	Silt	0
Wanganui—College Street	Silt	400
Wanganui—St. George Street	Silt	400
Wanganui—Gonville Street	Silt	200
Wanganui—Matheson Street	Silt	800
Wanganui—Campbell Street	Silt	400
Wanganui—St. John's Hill	Silt	400
Wanganui—St. John's Hill	Silt	400
Aramoho—Foothills	Sandstone-marl	1,600
Aramoho—Foothills	Sandstone-marl	1,600
Aramoho—Foothills Cumbrae Race	Sandstone-marl	1,200
Aramoho—Kaikoukoupu Road	Sandstone-marl	2,600
Aramoho—River Bank	Silt	400
Patea	Silt	1,000
Patea	Silt	2,400
Taranaki:		
Hawera	Silt	6,800
Hawera	Silt	7,200
Stratford	Andesite	3,600
Inglewood	Andesite	9,000
Opunake	Andesite	4,800
Omeho	Andesite	28,000
New Plymouth	Andesite	36,000
Waitara	Andesite	26,800
Clifton	Andesite	27,000
Taumaranui District:		
Taumaranui	Silt	2,000
Taumaranui	Silt	1,000
Taumaranui	Silt	800
Taumaranui	Silt	400
Hikimutu	Silt	2,000
Hikimutu	Silt	2,000
Hikimutu	Silt	1,600
West Coast District:		
Kopaki	Rhyolite	2,000
TeKuiti	Silt	800
Waitomo	Limestone	2,800
Waitomo	Limestone	4,600
Waikato and Piako Valleys:		
Te Awamutu	Silt	8,600
Te Awamutu	Silt	10,600
Frankton	Silt	400
Hamilton (1 mile N.)	Silt	0
Hamilton (1 mile S.)	Silt	7,400
Hamilton (1 mile E.)	Silt	1,000
Hamilton (1 mile W.)	Silt	3,500
Cambridge	Silt	5,200
Putaruru	Silt	6,800
Putaruru	Silt	300
Putaruru	Silt	100
Morrinsville—North	Silt	9,800
Morrinsville—South	Silt	800
Morrinsville—East	Silt	16,000
Morrinsville—West	Silt	6,800
Nagata	Silt	600
Paeroa	Silt	1,000
Hikutaia	Silt	200
Orongo	Silt	3,600

Locality	*Geology*	*Iodine, parts per billion*
Rotorua and Taupa District:		
Rotorua—Gardens	Rhyolite	1,600
Rotorua—Government grounds	Rhyolite	1,400
Rotorua—Hospital	Rhyolite	800
Toupo	Rhyolite	800
Tokaanu	Rhyolite	600
Bay of Plenty:		
Maungapohatu	Rhyolite	400
Ruatahuna	River sand	200
Ruatahuna	Rhyolite	400
Poroporo	Swamp	9,200
Thornton—River Swamp	Swamp	1,000
Thornton—Peaty	Swamp	1,000
Thornton—Peaty	Swamp	800
Thornton—Gritty	Swamp	600
Thornton—Clay	Swamp	400
Pongakawa	Silt	1,000
Te Puke	Silt	1,000
Tauranga	Silt	5,200
Cape Colville Peninsula:		
Waihi	Rhyolite	600
Thames	Silt	600
Thames	Silt	4,200
Mercury Bay	Rhyolite	0
Coromandel	Andesite	1,200
Auckland District:		
Mercer	Basalt	22,400
Pukehoe	Basalt	24,000
Onehunga (a)	Basalt	6,800
Onehunga (b)	Basalt	8,000
Onehunga (c)	Basalt	1,600
Onehunga (d)	Basalt	5,600
Auckland—Domain	Basalt	3,400
Auckland—Mount Eden	Basalt	6,200
Auckland—One Tree Hill	Basalt	25,600
Belmont School	Sandstone	2,300
Takapuna	Basalt	3,400
North Auckland Peninsula:		
Helensville (a)	Dune sand	600
Helensville (b)	Dune sand	4,600
Helensville (c)	Dune sand	6,200
Helensville (d)	Dune sand	6,200
Wellsford	Marl-limestone	200
Port Albert	Marl-limestone	600
Paparoa	Marl-limestone	400
Dargaville	Dune sand	200
Dargaville	Dune sand	400
Titoki		7,400
Poroti	Basalt	30,400
Waipu	Marl	1,200
Whangarei (½ mile S.E.)	Silt	1,000
Whangarei (½ mile S.W.)	Silt	600
Whangarei (½ mile N.E.)	Silt	600
Whangarei (1½ miles N.W.)	Basalt	70,000
Glenbervie	Basalt	33,000
Kiripaka	Paleo-mesozoic	400
Kauri	Basalt	9,600
Ruatangata—East	Basalt	8,200
Ruatangata—West	Basalt	8,800

Locality	*Geology*	*Iodine, parts per billion*
North Auckland Peninsular:		
Purua	Marl	200
Hikurangi	Marl	800
Ngararatunua	Basalt	12,400
Whakapara	Marl	400
Riponui	Marl	600
Hukerenui	Marl	400
Opua	Paleo-mesozoic	400
Ohoeawai	Basalt	8,400
Oue	Marl	200
Rawene	Marl	0
Kohukohu	Marl	200
Motukaraka	Marl	400
Takahue	Marl(?)	200
Herekino	Marl(?)	400
Kaiataia	Clay	200
Rangitihi	Silt	200
Victoria Valley	Silt	400
Waipapakauri	Silt	0
Awanui	Silt	1,000
Kaeo	Paleo-mesozoic	400
Peria	Basalt(?)	1,900
Fairbarns	Marl(?)	200
Totara North	Paleo-mesozoic	1,400
Mongonui		1,200
Outlying Islands:		
Chatham Islands	Swamp	10,400
Raratonga	Basalt	8,000

It will be observed that rhyolitic soils are deficient in iodine. The curve in figure 6 shows the relation of soil iodine to goiter in school children.

VI. Iodine content of salt and sea water. Since all salt deposits are the result of evaporation of either sea water or the water of inland salt lakes it is perhaps more logical to consider the iodine content of sea water first. The old analyses were rather inaccurate. In 1895, Winkler (86) determined the iodine content of the Adriatic, finding 38 parts per billion. In 1899 Gautier (87) found 23 parts per billion of Atlantic ocean water. He filtered surface water of the Atlantic ocean through porcelain and could detect no inorganic iodine in the filtrate but found iodine in organic combination in the filtrate. Most of the iodine, however, was in the body of the organisms held back by the filter. In the Mediterranean he analyzed the water at different depths down to 980 meters and claimed that the *total* iodine was the same at all depths. In the surface there was no *inorganic* iodine. In the deepest samples there was very little iodine in organisms. Thorpe (88) in 1912 found only 4 parts of iodine per billion of Atlantic water. Von Fellenberg (89) found 17 in Mediterranean water and 14 in the English Chan-

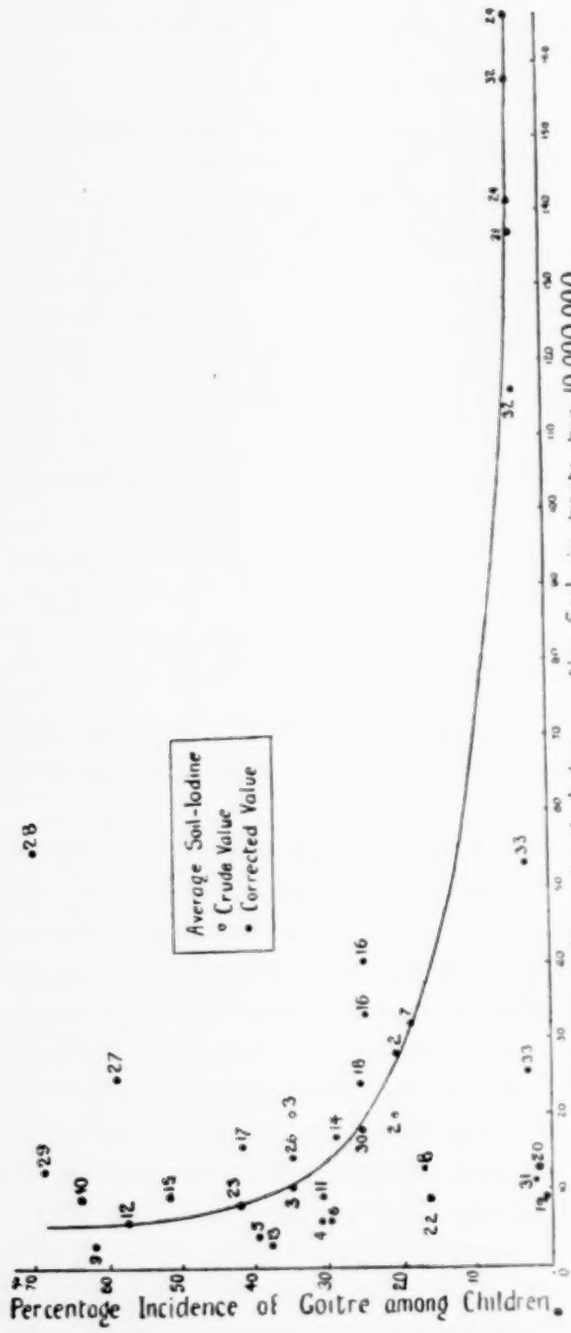
Average Soil-Iodine
o Crude Value
• Corrected Value
Percentage Incidence of Goitre among Children
Average Amount of Iodine in the Soil in parts per 10 000 000

Fig. 6. Curves showing the relationship between the average amount of the iodine in the soils and the regional incidence of goiter among school-children in New Zealand. The figures by dots denote the districts.

nel. Von Fellenberg (90) found an average of 23 parts per billion of sea water. Hercus, Benson and Carter (64) found 18 in the Pacific ocean near Dunedin, New Zealand. Determination of iodine in ocean water is somewhat difficult owing to the large amount of salt and the presence of dissolved silica and other colloidal material. The author (91) in 1922 found 50 parts per billion of water of Santa Monica Beach, California, but this water contained some decaying seaweed, which probably added to its iodine content locally. Water from the Great Salt Lake contained 70 parts per billion. Cameron (92), in 1922, found 25 parts per billion of water of the Strait of Georgia, British Columbia, the ratio of iodine to chlorine being 1 to 500,000. This is much less than the ratio of iodine to chlorine in most fresh waters, but is much more than the ratio of iodine to chlorine in the Great Salt Lake. It is probable that when the sea was first formed a large amount of chloride from the atmosphere was carried down in the first precipitation of water, whereas the iodine was so dilute in rocks that it was only released by the weathering of rocks. Much of the salt from the Great Salt Lake may have been due to leaching out of evaporated sea water from the sedimentary rock, the iodine being adsorbed by the porous rock and soil.

Erdmann (93) determined the iodine content of various salts as follows:

	Parts per billion
Kainit from Kalusc	870
Rock salt from Kossow	170
Rock salt from Bleicherode	10
Sylvian from Neustassfurt	42
Young rock salt	7.5
Sea salt from Berre	83
Mixed salt from Berre, more than	103
Carnallit	0

Winkler found iodine in sylvian but not in carnallit. Hercus, Benson and Carter (64) found 1400 parts of I_2 per billion of rock salt used in New Zealand. Krafft (94) in 1924 found iodine in salt from mines at Friedrichshall, Kochendorf. Fleissig (95) in 1922 examined the brine from which salt is made in Switzerland. No iodine was found in the salt of Bex and Rheinfelden. Von Fellenberg (96) in 1923 determined the iodine content of the salt from Schweizerhalle. At this place the brine was evaporated in a vacuum and after separation of the salt, the mother liquor was added to fresh brine thus concentrating the iodine, and therefore the iodine became concentrated in the salt. In August the salt contained no detectable iodine. On the 4th of September it contained 0.8 part per billion and in October it rose to 7.7 parts per billion. Some

of this salt purchased in Bérn contained 10 parts per billion. Salt from Bex contained 260 parts per billion. From the salt works in southern France fine salt from Dax contained 3½ parts per billion but none could be detected in that from Bérn. That from Briscons contained from 8 to 18 parts per billion. Sea salt contained from 1 to 10 parts per billion.

In regard to the retention of iodine in sea salt, it was shown by the author (91) that the iodine is nearly all lost by any ordinary method of preparation of the salt. When the salt is crystallized out the iodine remains in the mother liquor. If the total sea water is evaporated to dryness, when it becomes very concentrated, magnesium chloride is hydrolyzed forming free hydrochloric acid, and further evaporation leads to loss of iodine. In order to retain the iodine it was necessary to add enough sodium carbonate to completely precipitate all of the magnesium and remove this before evaporation. If the total iodine was retained there would be 2,000 parts of iodine per billion of salt. In the natural evaporation of arms of the sea and the formation of salt deposits the iodine is not uniformly distributed in the deposits but it is perhaps to a large extent retained by the soil and adds to the iodine content of the region.

Iodine has been detected in salt mines in Michigan. A review of this subject was made by Hayhurst (97) in 1922. During the Permian period an arm of the Pacific ocean was cut off by the rocky mountains and made an inland sea covering parts of South Dakota, Nebraska, Kansas, Oklahoma, Texas, and New Mexico. The artesian wells in Kansas are high in chlorine and iodine on this account. Mansfield (98) mapped out an area in Oklahoma, western Texas and southeastern New Mexico in which the layer of salt was probably more than 400 feet thick. This is a region of high iodine content and it is possible that much of the iodine was derived from evaporated sea water.

There are about seven million tons of salt used in the United States per year. A very small amount of this is used for human consumption.

In 1923–4 from the beginning of the winter to February 25, there were 450 tons of salt used in Minneapolis to keep the trolley switches open. Some of the iodine of salt that is applied to the ground is adsorbed by the soil. Some other salt deposits contain much higher iodine content than do NaCl deposits. It is especially true of the Caliche of Chile which consists chiefly of sodium nitrate but has a very high iodine content. Five hundred metric tons of iodine were exported from Chile in 1904. At that time iodine was recovered from the Caliche, at each refinery, only one year out of six in order to keep up the market price. The

possible output of the mines is 5,100 tons per annum. Von Fellenberg found 1,920 parts of iodine per billion of one sample of Chilien nitrate, but this is a mere trace of the amount found in the Caliche, of which it forms 200,000 parts per billion.

Ordinarily a person does not consume more than 10 grams of salt a day, which would supply about 0.02 milligram of iodine if the total iodine of sea water was retained. Since it is much easier to add iodine than to retain it in the purification of the salt, it is only in crude salt that the natural iodine content is of importance. This was emphasized by Marine in regard to the prevention of goiter in the sheep of Michigan by feeding crude salt which was begun about 1820.

VII. IODINE CONTENT OF DRINKING WATER. Von Fellenberg (96) determined the iodine content of drinking water of Bérn, Switzerland, in parts per billion. In June, 1922, it was 0.03, in August 0.02, in September 0.08, in November 0.36, and in January, 0.29. The iodine content of the water of Chaux-de-fonds was 1.4 and that of Sengau 0.07. He also made some determinations on river water. That of the Emme above Burgdorf was 0.38, that of the Aare above Bérn in December was 0.5, and in January 1.3.

McClendon and Williams (99), and McClendon and Hathaway (100) made the following determinations:

Iodine parts per billion	*Town*	*Source of water*
0.01–1.74	Minneapolis, Minn.	Mississippi
0.01	Duluth, Minn.	Lake Superior
0.01	Spokane, Wash.	Wells 60 feet deep
0.01	Rockford, Ill.	Wells 540–1,500 feet deep
0.012	Ames, Iowa	Wells 75–100 feet deep
0.012	Wellesley, Mass.	Wells 65 feet deep
0.015	Bozeman, Mont.	Bozeman Creek
0.015	Iowa City	Iowa River
0.15	Geneva, N. Y.	Seneca River
0.015	Milwaukee	Lake Michigan
0.02	Marquette, Mich.	Lake Superior
0.02	Indianapolis	White River and wells 365 feet deep
0.02	Seattle	Cedar River
0.03	Portland, Ore.	Bull Run Lake
0.05	Waseca, Minn.	Well 240 feet deep
0.05	Rochester, Minn.	Wells 32–418 feet deep
0.05	Hot Springs, Ark.	Spring
0.05	Lincoln, Neb.	Wells 77–100 feet deep
0.05	Wilmington, Del.	Brandywine Creek
0.06	Independence, Kan.	Verdigris River
0.06	Oregon City, Ore.	Clackamas River (glacial)
0.06	Cumberland, Md.	Mountain springs
0.08	Mount Clemens, Mich.	Wells 30–65 feet deep
0.08	Fargo, N. D.	Red River
0.09	Seattle	Cedar River
0.10	Winnetka, Ill.	Lake Michigan

Iodine parts per billion	*Town*	*Source of water*
0.10	Portland, Ore	Bull Run River
0.10	Hagerstown, Md.	Mountain springs and streams
0.10	Brunswick, Md.	
0.10	Hutchinson, Kan.	
0.11	Lawrence, Kan.	Shallow wells
0.12	Chicago	Lake Michigan at Wilson Avenue Crib
0.132	Raleigh, N. C.	Walnut Creek
0.14	Morris, Minn.	Well 70 feet deep
0.14	Norton, Mass.	
0.15	Charlestown, W. Va.	Spring
0.16	Thurmont, Md.	Mountain stream
0.18	Hancock, Md.	Mountain stream
0.18	Chippewa Falls, Wis.	Chippewa Springs
0.21	Columbus, Ohio	Scioto River
0.22	Nashville, Tenn.	Cumberland River
0.23	Miami, Fla.	
0.25	Harrisburg, Pa.	Susquehanna River
0.40	Frederick, Md.	Small stream
0.47	Morgantown, W. Va.	
0.60	Richmond, Va.	James River
0.61	Houston, Texas	Deep wells from 250 to 1,330 feet deep
0.66	Fort Scott, Kan.	Marmaton River
0.67	East Lansing, Mich	Well 400 feet deep
0.67	Chicago, Ill.	68th St. Crib
0.72	Washington, D. C.	Potomac River
0.72	Madison, Wis.	Wells
0.77	Denver	South Platte River, Cherry and Bear creeks
0.83	St. Paul, Minn.	Mississippi
0.84	Santa Barbara, Cal.	Wells
0.86	Cleveland, O.	Lake Erie
0.88	Linden, Calif.	Well 60 feet deep
0.90–12	Springfield, Ill.	Sangamon River and adjacent wells
0.92	Richmond, Va.	James River
1.05	North Chicago, Ill.	Deep well
1.07	Rochester, N. Y.	Hancock Lake
1.10	New York City	Catskill Supply (F. E. Hale)
1.19	Le Roy, N. Y.	
1.27	Greenville, Ill.	Deep well
1.30	New York City	Croton Supply (F. E. Hale)
1.45	Toronto	Lake Ontario
1.67	Charlottesville, Va.	
1.69	Kansas City, Kan.	Missouri River
1.74	New Haven, Conn.	Small lakes and rivers
2.30	Boston	Lake Cochituate, Sudbury and Nashua rivers
2.50	New York City	Long Island supply (F. E. Hale)
3.20	Atlanta, Ga.	Oconee River
3.52	St. Louis	Mississippi River
3.91	Salina, Kan.	Well
5.00	Baltimore	Gun Powder River
5.90	Berkeley, Calif.	San Pablo Lake
7.70	New Orleans	Mississippi River
44.69	Salt Sulphur Springs, W. Va.	Spring
54.58	Corona, Calif.	Source in Santa Ana Mountains
73.30	San Dimas, Calif.	Wells in river bed
105.80	Stanford, Calif.	Deep wells
184.70	Mexia, Texas	Deep well 3,005 feet

H. W. Clark in 1925 found that 80 Massachusettes water supplies averaged 2 parts iodine per billion.

McClendon, Hathaway, Vandersluis and Dahl (101) determined the iodine content of drinking water in Utah in relation to the percentage of goiter in schools as follows:

Iodine parts per billion	*City*	*County*	*Percentage goiter in schools*
0.01	Ogden	Weber	53.0
	Parowan	Iron	69.1
	Vernal	Uintah	40.8
	Nephi	Juab	64.3
	Kamas	Summit	46.4
	Park City		42.2
0.16	Salt Lake City	Salt Lake	41.6
0.18	Alpine		57.0
0.20	Midway	Wasatch	52.0
0.3	Utah Lake		
0.33	Syracuse	Davis	23.1
	Millcreek	Salt Lake	42.5
0.36	Oak City	Millard	82.2
0.4	Logan City	Cache	40.5
	Ft. Duchesne	Ninta	71.7
	Heber City	Wasatch	46.0
0.5	Murray	Salt Lake	34.4
	W. Warren		7.1
0.6	Brigham City	Boxelder	29.0
	Santaquin		45.0
	Butler School	Salt Lake	67.3
0.7	Farmington	Davis	54.5
0.2–0.7	Huntsville	Weber	41.1
0.6	Kaysville	Davis	49.1
0.9	Mt. Pleasant	Sampete	58.6
	Levan	Juab	73.4
2.16	Lakeview		6.0
2.5	Goshen		15.0
9.5	Milford	Beaver	23.0

Hercus, Benson and Carter (64) made the following determinations of iodine content of water in New Zealand:

Total iodine in potable water

New Zealand rivers:	*Parts per billion*
Clutha	0
Taieri	1.0
Leith	2.0
Springs derived from between Basaltic lavas near Dunedin:	
Maitland Street	8.0
Royal Terrace	4.0
Queen Street	2.0
Caversham	2.0
Artesian waters:	
Christchurch	0
New Brighton	0
Heathcote	2.0
Hastings	20.0
Napier	16.0

Eldridge (102) was unable to determine the iodine content in surface

waters of Michigan but made the following determinations of iodine in ground waters:

Counties	*City or village*	*Iodine parts per billion*
Allegan	Allegan	None
	Otsego	None
Alpena	Lake Huron-Alpena	0.4
Barry	Hastings	Trace
Berrien	Benton Harbor	0.6
	Niles	2.0
	St. Joseph	0.5
	Three Oaks	None
	Watervliet	None
Branch	Coldwater	0.8
Calhoun	Albion	2.38
	Marshall	None
Chippewa	Sault Ste. Marie	None
Delta	Escanaba	0.3
Eaton	Charlotte	Trace
Genesee	Flushing	8.2
	Flint-river	None
Gladwin	Gladwin	0.6
Gogebic	Ironwood	None
Grand Traverse	Traverse City	None
Gratiot	Alma	0.6
Houghton	Calumet	None
	Chassell	None
	Houghton	None
	John Doelle Ag.	None
	Houghton	None
	Hubbell	None
	Lake Linden	None
	South Range	None
Huron	Bad Axe	Trace
	Elkton	1.2
Ingham	Lansing	1.0
	East Lansing	0.7
Ionia	Ionia	Trace
Isabelle	Mt. Pleasant	4.0
Jackson	Jackson	None
Kalamazoo	Kalamazoo	2.2
Kent	Grand Rapids	0.8
Lapeer	Almont	3.9
	Lapeer	None
	Otter Lake	Trace
Livingston	Howell	0.7
Luce	Newberry	None
Macomb	Mt. Clemens (min. spring)	3,100.0
	Mt. Clemens	28.0
	Mt. Clemens	3.0
	Mt. Clemens	20.0
	Richmond	Trace
	Romeo	None
	Utica	1.0
Marquette	Marquette	None
	Negaunee	None
	Lake S.	0.10
Mason	Ludington (Lake Mich.)	0.4

Counties	*City or village*	*Iodine parts per billion*
Mecosta	Big Rapids	1.3
Menominee	Powers	None
Midland	Coleman	Trace
	Midland	0.7
	Midland	18.0
	Midland (Dow)	12.0
	Midland (Barth)	11.6
	Sanford	1.4
Monroe	Dundee	0.6
	Monroe	Trace
Ogemaw	West Branch	None
Ontonagon	Ontonagon	None
Otsego	Gaylord	None
	Gaylord	None
Ottawa	Holland	Trace
Saginaw	Chesaning	9.1
	Saginaw	68.16
	Saginaw	92.3
	Saginaw	34.0
	Saginaw	32.5
	Saginaw	12.0
	Saginaw	91.0
	Saginaw	22.1
Sanilac	Sandusky	1.9
Shiawassee	Owosso	5.0
	Owosso	1.3
St. Joseph	Three Rivers	Trace
Tuscola	Vassar	0.9
Van Buren	Paw Paw	None
Washtenaw	Ypsilanti	1.2
Wexford	Cadillac	2.4
	Cadillac	0.86
	Harlan	None
	Harriette	None
	Manton	None
	Mesick	None
Wayne	Huron Twp.	65.0

Reichert and Trelles (103) determined the iodine content of underground water of the Argentine Republic. Meisbach (104) supposed that the low iodine content of the waters of Bavaria was the cause of goiter. Hickethier and Jacobucci (105) determined iodates in the waters of northern Santa Fe. Forman (106) in 1925 determined the iodine content of the public water supply of New Jersey, finding 0–8 parts per billion.

Von Fellenberg (107) determined the iodine content of Swiss mineral waters as follows:

Spring

	Iodine parts per billion
Passing, Theophil	18
Passing, Belvedra	41
Passing, Helenen	227
Passing, Ulricus	760

	Iodine parts per billion
Passing, Fortunatus	1,005
Wildig's Iodine water	6,310
Rothen	12

H. L. Ferguson determined the iodine content of Illinois waters in parts per billion as follows: Springfield 9.8–13.3, Rockford 3.4, Harrisburg 1.3, Elgin 1.2, Freeport 0.8, but found none at Quincy, Decatur, Danville, Jackson, Effingham and Cairo.

VIII. Iodine content of the atmosphere. Gautier (87) determined the iodine content of the air and found all the iodine in bodies of micoörganisms or other dust particles. Preliminary experiments by the author's students tend to confirm this.

Von Fellenberg (96) found a very low iodine content of air, about 0.04 milligram per thousand cubic meters of air. Von Fellenberg (108) determined the iodine content of air at various heights above the ground and found larger amounts than previously, from 0.09 to 2.54 milligrams per thousand cubic meters of air. His highest determination was, however, the first one and was never duplicated. As to the source of iodine in the air Von Fellenberg (109) determined the evaporation of iodine from sea water and found it to go on at a considerable rate, sea water in the bottom of a desiccator losing up to 8 per cent of its iodine in 26 days.

Von Fellenberg, Geilinger and Schweizer (110) determined the rate of evaporation of iodine from the soil, They had already shown that iodine comes out of the soil but in order to compare different soils they added potassium iodide to them and then determined the rate at which iodine evaporated. It was found that calcium and magnesium carbonates had no effect on the oxidation of iodide. The iron content and the pH had an effect, however. They determined the "specific catalytic action" of the soil after removal, by hydrochloric acid, of soluble constituents, in determinations of the parts per billion of iodine coming out of the soil in 24 hours after wetting it with 2 per cent potassium iodide:

	Specific catalytic action	*pH.*
Oolite, Hornussen	2,300	
Oolitic earth	4,940	8.00
Molas, marine Hunzenschwil (soil)	620	5.03
Molas, fresh water Hunzenschwil (sand)	310	
Diluvium, Liebefeld (soil)	950	6.32
Dolomite, Kaisten (weathered)	320	
Dolomitic soil	820	8.37
Marl, Effingen	7,830	
Effingen strata, soil	11,900	8.19
Muschelchalk, Kaisten (weathered)	540	
Muschelchalk (soil)	1,970	8.06

IX. IODINE CONTENT OF PLANTS. Bourcet (111), (112) analyzed twenty-eight plants that grew in the same kind of soil (which contained 830 parts per billion of iodine). He found in the potato family 0 to 0.7, in the Cucurbitacea 0 to 0.017, in the Cruciferae 0 to 0.24, in the Chenopodia 0.021 to 0.38, in the legumes 0.013 to 0.32, in the lilies 0.12 to 0.94, in the Polygonum 0.047, in the umbels 0 to 0.14, in the Synanthrea 0 to 0.96. In 1919 Winterstein (113) studied the iodine content of plants, and states that iodine is only accidentally found in vegetable material. In thirty flowering plants he found iodine in traces in five, which were beets, potatoes, lettuce and carrots. He used 10 to 50 grams air-dried material.

Numerous papers on the relation of seaweed to goiter have been published.

Hendrik (114) found in the stem of the seaweed Laminaria Digitata 0.094 per cent and in the leaves 0.084 per cent. Other seaweed contains somewhat less. Loew (115) observed that goiter and cretinism are unknown in Japan, where they eat seaweed. Burd (116) gives some modern work on the iodine value of kelp. Shkatelov (117) found 0.06 per cent NaI in the ash of sea weed from the Black Sea. Freundler, Manegèr and Laurent (118) found about one-half of 1 per cent iodine in Laminaria from the coast of France.

According to Stoklasa (119) iodine is beneficial to plants. In his experiments and those of Von Fellenberg and Schmid (120), the plants were fertilized with potassium iodide solution. Forbes and Beegle (121) attempted to determine the iodine content of various food materials. The samples were too small for accurate work but the presence of iodine was determined in a large number of plants. Some of the samples, however, were too small to detect any iodine in them. They arranged food in order of increasing iodine content as follows: nuts, spices, fruits, cereals, hay, garden vegetables and leguminous seeds. Bohn (122) made further determinations using too small samples for accurate work.

Von Fellenberg (96) determined the iodine content, in parts per billion, of food from a less goitrous region, Chaux-de-Fonds, and a more goitrous region (Signau) in Switzerland, as follows:

Food	*Chaux-de-Fonds*	*Signau*
Beet	15	10
Carrot	7	5
Red cabbage	61	21
Potato peeled	7	4
Potato unpeeled	18	11

Food	Chaux-de-Fonds	Signau
Rhubarb stem	10	3
Apple	7	2
Apple cored	6	1
Apple cores	32	19
Hay	47	80

Von Fellenberg and Geilinger (123) determined the iodine absorption by fungi, making cultures in media containing one-half per cent of potassium iodide in 0.003 per cent of starch. In acid solution the oxygen of the air oxidized the iodide to iodine. On adding bacteria this iodine disappeared and Von Fellenberg supposed that it was absorbed by the bacteria but we know particularly from the work of W. M. Clark that certain bacteria, at least, have a powerful reducing action and reduce free iodine very rapidly. Von Fellenberg's evidence that the bacteria had absorbed iodine was based on the fact that they contained iodine after removal from the culture medium, but the culture medium contained one-half per cent of potassium iodide and the dried bacteria contained only about one-half per cent of iodine. The dried substance was less than one-fourth of the total weight of the bacteria. Further experiments were done with mold as shown in the following table:

Iodine binding by Aspergillus niger and albumin at different pH values

	Iodine in fresh substance	Iodine in dry substance
	parts per billion	
1. Aspergillus niger	11	45
2. Aspergillus niger + KI	625	2,800
3. Aspergillus niger + KI + powdered chalk	40	180
4. Egg albumin + KI + lactic acid	500	6,550
5. Egg albumin + KI	0	0

Von Fellenberg concluded that iodine was bound by mold in the same way as by egg white.

McClendon and Hathaway (100) in 1924, determined the iodine content of food from goitrous and non-goitrous regions as follows:

Iodine, parts per billion—dry foodstuff from non-goitrous regions

	Iodine content	Locality
Wheat	4	Storrs, Conn.
Wheat	9.3	Edgecomb, Me.
Oats	23	Storrs, Conn.
Oats	175	Wiscosset, Me.
Corn	52	Wiscosset, Me.
Barley	73	Storrs, Conn.
Rye	3.5	Storrs, Conn.
Carrots	170	California Coast
Cranberries	100	Cape Cod (123)

From goitrous regions

	Iodine content	*Locality*
Cereals:		
Oats	10	Minnesota
Wheat	1	Minnesota
Wheat	6.6	Minnesota
Straight flour	3.5	Minnesota
Bran	15.5	Minnesota
Shorts	9.6	Minnesota
Red dog	3.7	Minnesota
Pot herbs:		
Spinach	19.5	Oregon
String beans	29	Oregon
Carrots	2.3	Oregon
Soup vegetables	13.5	Oregon
Fruits:		
Apples (peeled and cored)	3	Oregon
Pears (peeled and cored)	15	Oregon
Prunes	4.8	Oregon
Bing cherries	33	Oregon
Peaches	11.1	Oregon
Loganberries	160	Oregon
Cranberries	0	Minnesota

Von Fellenberg (83) determined the iodine content of Lichens which he claims obtain iodine from the air, and of fresh water of Algae, as follows:

Lichens

	Parts per billion
1.	140
2.	200
3.	300
4.	480
5.	310
6.	310
7.	240
8.	500

Algae

	Parts per billion
9. Protococcus viridis	2,420
10. Protococcus viridis	1,560
11. Protococcus viridis	980
12. Spirogyra	340
13. Vaucheria	3,440
14. Algae	7,300
15. Algae	8,350

Von Fellenberg (107) determined the iodine content of various plants as follows:

Cereals and legumes

	Parts per billion
Wheat—United States, Hanley, Minn	64
Wheat—United States, Elkon, Tex	48
Wheat—Manitoba	56
Wheat—Manitoba	26
Wheat—Australia	44
Wheat—Roumania	28
Wheat—Switzerland, Geneva	26
Wheat—Switzerland, Bern	12
Wheat—Switzerland, Zurich	40
Rye—Switzerland, Bern	60
Rye—Switzerland, Waadt	24
Rye—Switzerland, Zurich	20
Oats	36
Grünkern	24
Maize—Italian	12
Rice—Italian	32
Rice—Indian	10
Broken Rice	8
Barley	22
Tapioca	12
Sago	42
Yellow peas	64
Lima beans	24

	Parts per billion
Lentel	16
Chestnuts	15
Fruits	
Lemons—Italian, juice	16
Lemons—Italian, whole	7
Lemons—Italian, juice	16
Lemons—Italian, whole	9
Lemons—Italian, juice	45
Oranges—Italian, peeled	6
Mandarinen—peeled	8
Mandarinen—peeled	6
Bananas—peeled	29
Bananas—peeled	28
Grapes—Spanish	120
Dry prunes—Serbian	100
Fungi	
Fungi	6
Fungi	70
Fungi	7
Fungi	43
Oils	
Olive oil	66
Peanut	30
Sesame	30
Almond	50
Poppyseed	33
Castor oil	43
Linseed oil	54
Cocoa butter	87
Cocoanut oil	95
Nuts	
Hazelnut	15
Walnut	30
Almond	20
Spanish peanut	200
Cocoa and chocolate	
Cocoa	80
Chocolate	30
Chocolate	80
Milk chocolate	140
Milk chocolate with coffee	120
Chocolate a la noisette	60
Drinks	
Tea—Ceylon	80
Green tea—China	73
Mate—Brasilian	160
Coffee	80
Linden blossoms	75
Camomile	94
Valerian roots	232
Island moss	310

X. IODINE CONTENT IN ANIMALS. Drechsel (124) in 1896 isolated an organic iodine compound out of the skeleton of gorgonians (seafans). He called the organic skeletal matter "gorgonin" and the isolated compound "iodogorgonic acid." The latter contained nearly 8 per cent of iodine. Drechsel thought it was iodamino-butyric acid but Wheeler and Jamieson (125) in 1905 succeeded in synthesizing it by the action of iodine on l-tyrosine in alkaline hydroxide solution and determined its composition to be di-iodotyrosine. This compound and thyroxin are known to occur in animals, and iodized fats are supposed to occur in them, as well as inorganic iodine compounds.

Bourcet (111) determined the iodine content of fish and other sea food as follows:

		Parts per billion
Clupea harengus	herring, smoked, roe	800
Clupea harengus	herring, smoked, milt	600
Clupea harengus	herring, smoked, entire	1,700
Clupea harengus	herring, smoked, entire	1,800
Clupea harengus	herring, smoked, entire	2,000
Gryphea arcuata	Portuguese oysters	1,300
Raja clavata	Ray	200
Merlangus vulgaris	Whiting	300
Scomber scombrus	Mackerel	300

		Parts per billion
Alosa sardina	Salt sardines	600
Trigla cuculus	Gurnard	1,200
Mytilus edulis	Mussel	1,900
Cadus morrhua	Salt cod	1,200
Merlangus corbonarius	Coal fish, viscera	2,400
Merlangus corbonarius	Coal fish, flesh	900
Crangon vulgaris	Shrimp	700
Littorina littorea	Periwinkle	750
Alburnus lucidus	Bleak	600
Auguilla vulgaris	Eel	800
Esox lucius	Pike	300
Leuciscus rutilus	Roach	1,200
Gobio fluviatilis	Gudgeon	120
Abramis brama	Bream	1,200
Lotta vulgaris	Burbot	800
Salmo salar	Atlantic salmon, head	1,400
Truita marina	Salmon trout	100
Cyprinus carpio	Carp	600
Leuciscus cephalus	Chevenne	70
Chondostromum nasus	Mullet	600
Bolva vulgaris	Ling	1,200

McClendon and Hathaway (100) determined the iodine content of skimmed milk from Minnesota (a goitrous region) to be 12 parts per billion on a dry basis and of butter, 140. From this it may be calculated that fresh milk contains about 7 parts per billion of iodine of which 6 parts is in the butter fat and one in the skimmed milk. A sample of goat's milk from the California coast, which is a non-goitrous region (Salinas) yielded 400 parts per billion of iodine on the dry basis, indicating that the iodine content of milk varies with the locality.

Von Fellenberg (96) determined the iodine content of some animal foods purchased in Switzerland as follows:

	Origin	*Iodine parts per billion*
Milk, eggs and meat:		
Milk	Bern	5
Butter		106
Skim milk cheese		38
Eggs	Wengi, See land	22
Eggs	Italy	12
Eggs	Steiermark	63
Eggs	Bulgaria	27
Veal	Bern	22
Beef	Bern	5
Ox liver	Bern	19
Water animals:		
Trout	Bern Market	36
Perch	Bern Market	29
Sardines—Market "Amieux" headless	Mediterranean	163
Tuna	Mediterranean	53
Bath sponge	Greece	3,870,000
Fat and oils:		
Lard	America	7
Cod liver oil, refined	Scandinavia	7,200
Cod liver oil, crude	Scandinavia	3,370

Tressler and Wells (126) determined the iodine content of animals from the sea and fresh water in the United States as follows:

	Iodine parts per billion	
	Fresh	*Dry*
Mollusks:		
Clams, hard—*Venus mercenaria*	1,370	6,200
Oysters, select—*Ostrea Virginica or Ostrea elongata*	1,160	6,000
Oyster juice, from "selects"	120	3,170
Scallops, giant—*Plactopecten grandis*	150	810
Crustaceans:		
Crabs, blue, soft, whole—*Callinectes sapidus*	90	490
Crab meat flake—*Callinectes sapidus*	180	870
Lobster—*Homarus Americanus*	1,380	11,590
Shrimp, headed	450	2,250
Mammal:		
Whale steak, canned	<10	<40
Marine Fish:		
Bluefish—*Pomatomus saltatrix*	260	1,870
Cod—*Gadus callarias*	240	1,000
Haddock—*Melanogrammus aeglefinus*	290	1,050
Halibut—*Hippoglossus hippoglossus*	250	830
Mackerel, Boston—*Scomber scombrus*	140	330
Mackerel, Spanish—*Scomberomorus maculatus*	400	1,410
Pollock—*Pollachius virens*	120	900
Pompano—*Trachinotus carolinas*	80	250
Scup—*Stenotomus chrysops*	300	950
Spot—*Leiostomus Xanthurus*	590	1,140
Squeteague—*Cynoscion regalis*	230	850
Tautog—*Tautoga onitis*	270	1,170
Winter flounder—*Pseudopleuronectes americanus*	180	730
Anadromous fishes:		
Alewives smoked—*Pomolobus pseudoharengus*	260	500
Rock—*Roccus lineatus*	450	2,000
Smelt—*Osmerus mordax*	10	70
Spotted squeteague—*Cynoscion nebulosus*	20	80
White perch—*Merone americana*	420	1,420
Fresh water fishes from Lake Erie:		
Cisco, smoked	240	550
Cisco roe, smoked	270	870
Lake trout, *Salvelinus namaycush*	10	40
Whitefish, *Coregonus clupeiformis*	30	110
Fresh water fishes from Potomac River:		
Bass, large mouth black—*Micropterus salmodes*, lacepede	50	190
Perch, yellow—*Perca flaverscens*	20	90
Pickerel, eastern—*Lucius reticulatus*, Le Sueur	70	300
Fresh water fishes from Mississippi River at Fairport, Iowa:		
Bass, large mouth black—*Micropterus salmoides*	10	40
Black bullhead—*Ameriurus melas*	10	40
Blue gill—*Lepomis incisor*	40	180
Bowfin—*Amiatus calva*	20	80
Buffalofish, big mouth—*Ictiobus cyprinella*	20	80
Buffalofish—*Carpiodes difformis*	30	130
Buffalofish, razor back—*Ictiobus bubatus*	20	80
Carp—*Cyprinus carpio*	10	40
Channel catfish—*Ictaluras punctatus*	10	40
Drum, fresh water—*Aplodinotus*	<10	<40

	Iodine parts per billion	
	Fresh	*Dry*
Grunniens:		
Gar pike—*Lepisosteus osseus*	10	40
Gizzard shad—*Dorosoma cepedianum*	10	40
Spotter sucker—*Minytrema melanopes*	<10	<40
White crappie—*Pomoxes annularis*	10	30

Jarvis, Clough and Clark (127) determined the iodine content of salmon, classified according to species, that average as follows:

Iodine content canned salmon by species

	Parts per billion dry basis
Steelhead	1,314
Red, Sockeye, Blueback	1,261
Chinook, King (1 and 2)	1,086
King—All grades	975
Pink	940
Chum	812
Coho	781
Atlantic	628

Iodine content canned Chinnok Salmon by districts

	Parts per billion Dry basis
Columbia River	1,559
Bristol Bay	1,438
Central Alaska	1,421
Puget Sound	1,039
Wedderburn	957
Klamath River	906
S. E. Alaska	894
Yukon	769

Kendall found the iodine content of human blood to vary from 0.01 to 0.017 mgm. per 100 cc., the average being 0.013.

The effect of iodine compound on the metamorphosis of tadpoles. Gudernatsch (128) observed that the feeding of mammalian thyroid gland to tadpoles of frogs and toads, caused them to stop growing and very rapidly develop into frogs or toads which were of small size owing to their precocious development. This phenomenon was studied by a number of workers and it was found that the thyroid was not the only substance which would produce this metamorphosis, but other iodine compounds were also effective.

Morse (129) observed that iodized serum albumin was also effective. Therefore, one would suppose that the injection of iodine directly into the blood, since it would lead to the formation of iodized serum albumin, would be effective. Swingle (130), in 1922, observed that any iodine preparation which he tried was effective, but the effect was not simply due to the iodine content, because it was not proportional to the iodine content. In order to rule out the effect of the thyroid gland of the tadpole itself he cut this out and verified by microscopic sections later that he had produced a complete thyroidectomy. Thyroidectomized tadpoles never metamorphose unless fed iodine preparations. In order to produce metamorphosis, thyroid feeding was the most effective. Di-iodotyrosine was next in order and potassium iodide was least ef-

fective. That is, it was effective only if given in great excess. These experiments were done on frog tadpoles but the tadpoles of salamanders behaved similarly. Axolotls were thyroidectomized and then injected with di-iodotyrosine which produced metamorphosis. Necturus (131) is a related species which never metamorphoses. It is not possible to cause it to metamorphose by means of thyroid. Romeis (132) states that thyroxin is 100 times as effective as di-iodotyrosine.

XI. Iodine absorption. Von Fellenberg (83) states that in plants iodine may be absorbed from the atmosphere, to account for the fact that he found iodine in lichens growing on clean surfaces of rock. It is well-known that mammals absorb potassium or sodium iodide with extreme rapidity when taken by mouth. McLean (133) observed that when iodized fats are fed, the iodine is absorbed with the fatty acid and is deposited in the cells with the fraction containing the fatty acid, or "lipoid" fraction. If iodized albumen is fed the iodine is broken off from this combination and distributed in the same way that inorganic iodide is distributed in the body. Jess (134) studied the iodine content of cancer in a patient that had been given "alival," an organic iodine preparation, intramuscularly and "iodipin," another iodine preparation, by mouth. The blood contained 210,000 parts per billion of iodine, the thyroid 506,000, the cancer 210,000, the liver only 146,000, and skeletal muscle only 72,000.

McCarrison (135) interpreted experiments on animals in which the thyroid increased abnormally in size (goiter) as indicating failure to absorb the iodine from the food. He claims that large amounts of bacteria in the food or non-iodized fats or lime in the food caused goiter and, therefore, must have prevented the absorption of iodine. If fats became iodized in the intestine and then were not absorbed they would lead to the elimination of iodine in the feces. In the same way bacteria which passed out in the feces, if they had absorbed iodine in the alimentary tract, would prevent its absorption. It would be desirable, however, to determine this by iodine analyses. McClendon (136), in 1923, showed that bacteria removed iodine from the medium.

Besides iodine absorbed from the alimentary canal, iodine may be absorbed from the skin and lungs. Luckhardt, Koch, Schroeder and Weiland (137) observed that when iodine is deposited on the skin in the form of fumes it is absorbed and appears in the urine. When iodine fumes are inhaled they are absorbed. The toxic dose is 18 mgm. per kilogram of body weight (absorbed by the lungs), which causes a pulmonary edema. Wetzel and Sollmann (138) observed absorption of iodine through the skin.

XII. Iodine metabolism. In studying iodine metabolism it is desirable to know the total iodine intake. That is to say, that obtained from food, drink and breath and that absorbed through the skin. Since iodine was first discovered in marine products and since it was noted that a trip to the sea coast sometimes cured goiter, it has been supposed that proximity to the sea was one of the chief factors in the supply of iodine. In 1922, the author (139) pointed out that the sea water brought down on land (chiefly by the action of rain drops) has been determined by chlorine analyses in certain regions, particularly in New England and New York. The amount of iodine is very small. In fact one would have to be within about three miles of the coast to get much benefit. Right at the seashore iodine is brought ashore more in the bodies of seaweed or marine animals than by sea water that is washed ashore.

There is considerable goiter in Seattle, Washington which is right on the shore of Puget Sound. Apparently the width of the city itself is sufficient distance from the sea to decrease its beneficial effect. On the San Juan Islands in Puget Sound, there is practically no goiter among school children, showing the advantage of being entirely surrounded by the sea.

Hercus, Benson and Carter (64) showed that in Christchurch, New Zealand there was 20 per cent more goiter than in Christchurch Harbor (Lytleton) although the two cities are adjacent. In other words, a few miles separation from the sea decreases the availability of iodine from this source. Goiter occurs in England. In fact it has been called "Derbyshire neck." There is practically none in Scotland, which is narrower and therefore nearer to the sea than most of England. Goiter is uncommon in Denmark and in Norway, both of which are rather close to the sea. Holland may be divided into goiter-free and goiter-rich regions.

Perhaps the earliest experiments on iodine metabolism were attempts to produce goiter in animals by a low iodine intake. The earlier of these experiments concerned only the iodine in the water supply, thus Knappenburg (140) attempted to produce goiter in a goiter-free region of Holland by supplying rats with water (brought from the city of Utrecht) which had a low iodine content. He reported negative results. However, the Utrecht Goiter Commission stated that the water did have an effect on the weight of the thyroids.

Houssay (141) performed similar experiments in Buenos Aires by giving rats water brought from a goiter region and he states that only

two rats (out of several lots of 20 each) developed goiter. These experiments can be criticised owing to the fact that the iodine content of the food was not determined.

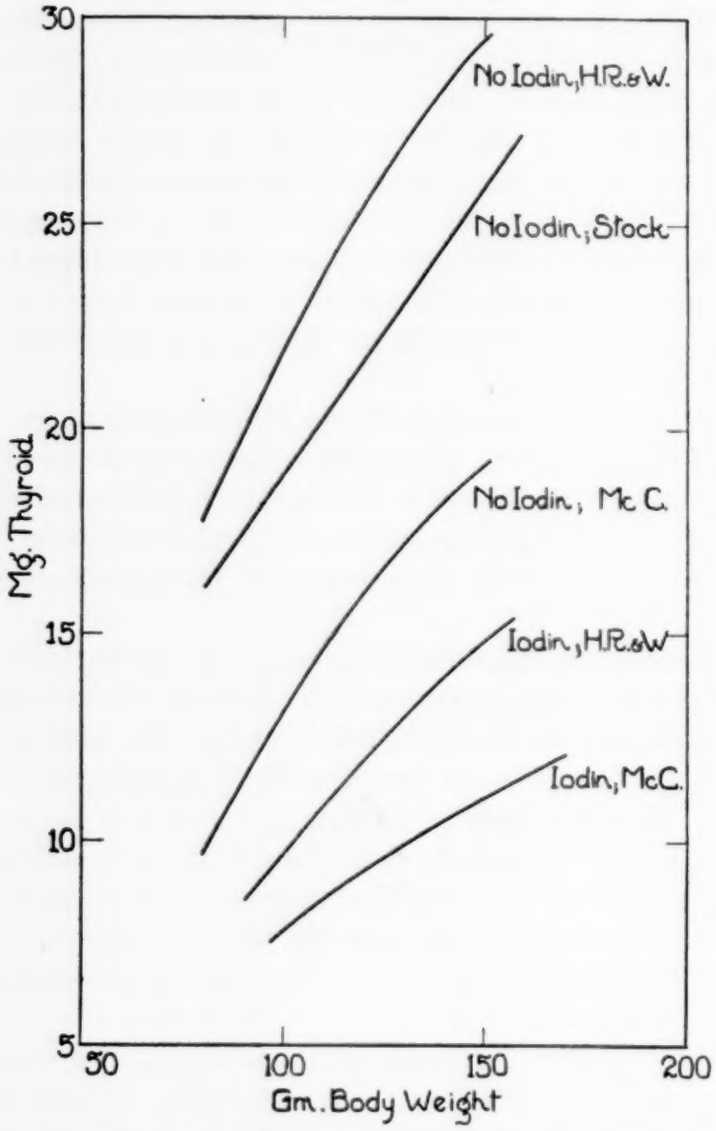

Fig. 7. Relation of weight of thyroid in milligrams to body weight of white rats in grams, on low (no iodine) and high (iodine) diets.

McClendon and Williams (142) performed experiments on rats in which they state that the iodine content of the dry food was less than 120 parts per billion. More accurate analyses later showed it to contain 10 parts per billion of iodine. This diet contained casein from Grove City, Pennsylvania, creamery, containing only 6.7 parts per billion of

iodine. The rats receiving this low iodine diet and distilled water developed goiter, whereas control rats receiving the same diet and water containing 0.01 per cent iodine, had normal thyroids. The relation of the weight of the thyroid in milligrams to the body weight in grams is given in figure 7, in the two curves marked *iodine McC*, and *no iodine McC*. In these latter, the thyroid was not as large as in those of Dr. C. M. Jackson's rats (marked stock) receiving a low iodine diet, the iodine of which was not determined. Perhaps more careful experiments were made by Hayden, Wenner and Rucker (143), and their results are shown also in figure 7, in the two curves *iodine H. R. & W.* and *no iodine H. R. & W.* (The diet contained 9 parts per billion of iodine, as determined later.)

McClendon and Hathaway (144) analyzed the iodine intake in food and drink and the outgo in urine and feces of a normal man 23 years of age who had never developed an enlargement of the thyroid and yet was living in a goitrous region (Minneapolis). He consumed in three days 0.057 milligram of iodine on a diet which was as nearly as could be estimated his regularly accustomed diet. In these same three days he excreted 0.021 milligram of iodine, having retained 0.036 milligram of iodine, or a retention of 0.012 milligram per day. At this rate it would require about five years to accumulate 20 milligrams of iodine in the body, which is the quantity that Kendall has found to be the average body content of a normal man in this region. This excretion of 0.007 milligram of iodine per day is partly due to the fact that some of the iodine was contained in such substances as the seeds of fruits which were not digested and therefore gained no opportunity for the absorption of the iodine.

Von Fellenberg (145) performed an iodine metabolism experiment on himself, first on a low iodine intake of about 0.014 milligram of iodine per day, and later on a somewhat higher iodine intake, as shown in the following table:

Day	*Total iodine intake, mgm.*	*Urine*	*Iodine excretion, mgm.*			*Total elimination*
			Feces	*Nasal secretion*	*Sweat*	
1	0.0003	0.0086	—	—	—	0.0086
2	0.0143	0.0123	—	—	—	0.0123
3	0.0143	0.0186	—	—	—	0.0186
4	0.0143	0.0124	—	—	—	0.0124
5	0.0143	0.0209	—	—	—	0.0209
6	0.0143	0.0124	—	—	—	0.0124
7	0.0143	0.0123	—	—	—	0.0123
8	0.0143	0.0230	—	—	—	0.0230
9	0.0143	0.0122	—	—	—	0.0230
10	0.0143	0.0139	—	—	—	0.0139

Day	Total iodine intake, mgm.	Urine	Iodine excretion, mgm. Feces	Nasal secretion	Sweat	Total elimination
11	0.0143	0.0123	—	—	0.0063	0.0186
12	0.0143	0.0054	—	—	—	0.0054
13	0.0143	0.0115	—	—	—	0.0115
14	0.0143	0.0108	—	—	—	0.0108
15	0.0143	0.0092	—	—	—	0.0092
16	0.0143	0.0092	—	—	—	0.0092
17	0.0143	0.0048	0.0082	—	—	0.0130
18	0.0143	0.0139	0.0097	—	—	0.0236
19	0.0143	0.0102	0.0032	—	—	0.0134
20	0.0143	0.0139	0.0037	—	—	0.0176
21	0.0143	0.0208	0.0109	—	—	0.0317
22	0.0143	0.0108	0.0097	0.0013	—	0.0218
23	0.0143	0.0046	0.0060	0.0012	0.0050	0.0168
24	0.0143	0.0077	0.0030	0.0021	—	0.0128
25	0.0143	0.0092	0.0054	0.0033	0.0006	0.0185
26	0.0143	0.0085	0.0013	0.0019	0.0040	0.0157
27	0.0143	0.0070	0.0023	0.0029	0.0012	0.0134
28	0.0143	0.0051	0.0072	0.0006	0.0003	0.0132
29	0.0143	0.0044	0.0015	0.0014	0.0005	0.0078
30	0.0526	0.0132	—	0.0031	0.0039	0.0202
31	0.0526	0.0270	0.0093	0.0042	0.0027	0.0432
32	0.0526	0.0255	0.0026	0.0015	0.0039	0.0335
33	0.0526	0.0255	0.0177	0.0037	0.0029	0.0498
34	0.0526	0.0200	0.0052	0.0032	0.0025	0.0309
35	0.0526	0.0285	0.0027	0.0009	0.0009	0.0330
36	0.0526	0.0255	0.0035	0.0051	0.0024	0.0365
37	0.0557	0.0190	0.0031	0.0037	0.0036	0.0349
38	0.0719	0.0245	0.0077	0.0031	0.0017	0.0370
39	0.0719	0.0154	0.0040	0.0104	0.0019	0.0317
40	0.0719	0.0215	0.0025	0.0108	0.0022	0.0370
41	0.0719	0.0385	0.0153	0.0015	0.0013	0.0566
42	0.0719	0.0232	0.046	0.0006	0.0002	0.0286
43	0.0719	0.0177	0.0072	0.0095	0.0014	0.0358
44	0.0748	0.0207	0.0177	0.0041	0.0019	0.0444
45	0.0763	0.0575	0.0077	0.0036	0.0003	0.0691
46	0.0526	0.0430	0.0195	0.0058	0.0006	0.0689
47	0.0770	0.0293	—	0.0003	0.0055	0.0351
48	0.0770	0.0500	0.0170	0.0002	0.0003	0.0693
49	0.0770	0.0278	0.0642	0.0042	0.0008	0.0970
50	0.0143	0.0253	0.0033	0.0018	0.0130	0.0434
51	0.0143	0.0288	0.0068	0.0054	0.0037	0.0447
52	0.0003	0.0184	0.0004	0.0047	0.0018	0.0253
53	0.0003	0.0283	0.0004	0.0018	0.0005	0.0310
54	0.0143	0.0350	0.0029	0.0045	0.0031	0.0455

Von Fellenberg (146) determined the iodine in 24 hour samples of urine (about the first of November, 1923) of the citizens of Effingen, Hunzenschwil, and Kaisten. In Effingen there was 1 per cent goiter in the population, in Hunzenschwil there was 56 per cent and in Kaisten, 62 per cent.

Effingen

Sex	Age	Iodine, mgm.	Thyroid examination by palpation
Male	10	0.053	Normal
Female	34	0.028	Normal
Male	34	0.079	Normal

Sex	*Age*	*Iodine, mgm.*	*Thyroid examination by palpation*
Male	35	0.069	Normal
Male	36	0.073	Normal
Male	42	0.108	Normal
Male	44	0.040	Normal
		Kaisten	
Male	7	0.017	Slight enlargement
Female	13	0.014	Slight enlargement
Male	36	0.011	Medium adenoma
Male	37	0.025	Small adenoma
Female	37	0.025	Medium enlargement
Male	37	0.022	Slight enlargement
Female	40	0.024	Normal
Male	47	0.028	Slightly enlarged isthmus
Male	49	0.029	Slight enlargement
Male	67	0.014	Right lobe enlarged
Male	72	0.004	Right lobe enlarged
		Hunzenschwil	
Male	10	0.010	Slight enlargement
Male	12	0.008	About normal
Male	14	0.024	Slight enlargement
Male	19	0.007	Large goiter
Female	25	0.005	Left lobe, medium enlargement
Male	26	0.019	Right lobe, medium enlargement
Male	28	0.023	Right lobe, medium enlargement
Male	29	0.009	Slight enlargement
Male	30	0.022	Medium enlargement
Male	48	0.027	Normal
Female	64	0.028	Medium enlargement of isthmus
Male	72	0.021	Normal

Veil and Sturm (147) studied the variations in the iodine content of blood. In the late summer, and fall it was 128 parts per billion and in the winter, 83 parts per billion. About 65 per cent of the total iodine content of the blood was organic and 35 per cent inorganic. The distribution of iodine in the blood corpuscles and plasma was about 35 per cent in the corpuscles and 65 per cent in the plasma. If one-half gram of potassium iodide was given by mouth, about 68 per cent of it was excreted in the urine within 24 hours. The iodine of thyroidin taken by mouth behaved similarly. Of the 33 patients with goiter, 70 per cent of them had the iodine content of the blood below 120 parts per billion.

XIII. Prophylaxis in animals. Marine and Lenhart (148) observed that the addition of iodine to the water (1 part of iodine per million) in which young brook trout were being reared, prevented goiter in these animals. Control experiments without iodine showed goiter in a large number of the trout under the same conditions of water and food supply. Marine and Kimball (149) found that a milligram of iodine

per week given by mouth was sufficient to prevent goiter in a dog. As early as 1820, sheep growers in Michigan prevented goiter by the use of crude salt containing traces of iodine. Growers of sheep, hogs, goats, cattle and horses in Michigan, Wisconsin, Montana and Washington began giving domestic animals iodine or using crude salt which contained traces of iodine or iodized salt for goiter prophylaxis (150). Hart and Steenbock (151) advocate the use of foods higher in iodine content and where this is ineffective, to add 10 grains of KI to 100 pounds of feed for all brood sows in order to prevent goiter in the newborn (hairless pigs). Welch (152) found that 2 grains per day per animal was sufficient to prevent goiter. He states that the sheep-men (153) in Madison Valley, northwest of Yellowstone Park, added 0.03 per cent of iodine to salt for the sheep. The minimum quantity necessary is somewhat difficult to determine in field experiments since the natural sources of iodine are variable from year to year. Some years no goiter appeared even though no iodine was added.

Kalkus (154) reported on various stock animals in the state of Washington and showed, at least for angora goats, that goiter could be absolutely prevented by administering iodine during pregnancy, either by mouth, subcutaneously, or on the skin. Evvard, Lamb and Gassler (155) showed that potassium iodide would prevent goiter in lambs in Iowa. One-half grain of potassium iodide per week was fed to each mother. The elimination of iodine in the milk was practically complete 15 days after iodine feeding was stopped. No one has determined the minimum quantity of iodine necessary to prevent goiter in animals.

XIV. PROPHYLAXIS IN HUMAN BEINGS. In 1917, Marine and Kimball (156) experimented in the schools of Akron, Ohio; 2,190 school girls each took 2 grams of sodium iodide twice a year for 3 years. Of these only 5 developed goiter, while of the 2,305 girls not given iodine and observed as controls, 495 developed goiter. The result of this experiment was so striking and convincing that iodine prophylaxis for goiter was taken up in many parts of the United States, Europe, New Zealand and India. The administration of iodine for the prevention of goiter is under government control in Switzerland and Italy.

Coulaud (157) comments on the variability of the dose of iodine. In Switzerland about 1 milligram of sodium iodide is administered to each school child a week, whereas in America doses ten times this strong are used. In Switzerland, potassium iodide is added to common salt in proportion of 5000 parts per billion. He states that trials of iodine prophylaxis were made in France towards the middle of the last century

and later in Austria and Italy. The method, however, was soon abandoned, the heavy doses employed (from 1,000 to 1,500 parts per billion of table salt) having resulted in numerous accidents.

Von Fellenberg (158) determined the loss of iodine from salt after the addition of potassium iodide to it. The iodide is oxidized to iodine by nitrite, or by atmospheric oxygen under influence of catalysts, or the iodide without being oxidized diffuses in the moisture of the damp salt and finally reaches the bag in which the salt is contained and is concentrated by evaporation, and so is lost from the salt. The loss is very slow, however, and with certain samples of salt, no iodine was lost in 52 days.

Von Fellenberg (159) states that the consumption of iodide-salt in Switzerland reached 10,600 metric tons in 1925, and probably supplied two million of the population. Eggenberger (160) has written numerous papers on the use of iodized salt in Switzerland and enumerates the beneficial effects. He states that 0.04 to 0.08 milligram of iodine per day is the normal intake in goiter-free regions and that the biological minimum to prevent goiter is about 0.04 milligram per day. He estimates that after iodized salt had been used in Switzerland two and one-half years (reported in 1924) 17 per cent of the table salt used was iodized. In the region of Appenzell, 80 per cent of the table salt used was iodized. Iodized salt was introduced into Austria in 1923 by W. Von Jouregg, and in Bavaria in 1924 by Dieudonné. Hunziker, (161) 1924, has reviewed the whole question of goiter on the basis of iodine deficiency. The section of his book on *Iodized Salt* was written by Eggenberger. He also considers chocolate iodostarine tablets, containing 5 mgm. of iodine each, which have been used rather extensively in Switzerland. In these tablets the iodine is combined with an organic acid and flavored with chocolate. In some parts of Switzerland iodized salt is sold by the government and in other parts tablets containing iodine are issued in the public schools. He states that in cases where pregnant mothers have taken iodized salt there has been no goiter in newborns, and that endemic goiter is prevented by iodized salt. Many measurements on goiter patients have shown that all adolescent and many adult goiters slowly decrease in size where iodized salt is being used in the salting of all food and that less goiter operations have been necessary since it has been used. Neck measurements of school children by physicians show that goiters decrease in size by the use of iodized salt, or iodine tablets.

Silberschmidt (162) studied the use of iodized tablets (containing

½ mgm. of iodine) to reduce goiters in girls aged 15 to 22, and states that soft goiters reduced more rapidly than hard ones. Goiters with connective tissue infiltration are less likely to show much reduction from the iodized tablets or salt (Canton or Zurich).

Klinger (163) recommends one iodine (iodostarine) tablet per week for patients who have already been operated for goiter, to prevent recurrence. He reduced goiter incidence in school children from 90 per cent to 28 per cent in 15 months by 10 to 15 mgm. iodine per week. Oswald (164) recommends 1 to 2 mgm. of sodium iodide per week for each school child or pregnant woman. Hercus, Benson and Carter (64) report the results of prophylaxis in the schools of Christchurch, New Zealand, using the quantity of iodide advocated by Marine. At the end of three years 84½ per cent of the treated school children had normal thyroids, whereas only 57.6 per cent of the untreated school children had normal thyroids.

Little (165) increased the iodine content of the city water supply of Rochester, New York, by the addition of 16.6 pounds of sodium iodide every day for two weeks twice a year, to the upper part of Rush Reservoir. The iodine content of the city water was raised from the normal level of about one part per billion to 20 parts per billion by the end of two weeks, then dropped sharply, then remained at about 5 parts per billion, at least for many weeks. Quimby (166) advocates the selection of a municipal water supply of adequate iodine content, or if this cannot be done, the addition of iodine. Goodfellow (167) reviews the work on the addition of sodium iodide in water in Rochester, Ilkeston and Heanor. In the latter two towns the iodide is added continuously. At Ilkeston the consumption averages 1,600 gallons per day and two pounds of sodium iodide is added per week. Sherman (168) added two pounds of sodium iodide to the city water supply of Sault Ste. Marie, Michigan, every day for two weeks twice a year. Ellms (169) estimated that the cost of adding 75 parts per billion of sodium iodide to city water would be $2.83 per million gallons. Hathaway (170) advocates iodine surveys of all goitrous regions, the addition of sodium iodide to the water supplies of cities and towns, and the use of iodized table salt or tablets in rural communities.

Rich (171) discussed the question of iodine in the water supply in Michigan and described the administration of iodine in table salt. Grau (172) in 1923 described a method of bacteriological sterilization of drinking water by adding to a litre, 5 drops of 8 per cent tincture of iodine, allowing it to stand twenty minutes, then adding 5 drops of 15

per cent sodium thio-sulphate solution. This is similar to the method of sterilization of water with chlorine as used in the U. S. Army. Major Hitchens, M.C.U.S.A. (173) dispenses with the use of thiosulphate by reducing the iodine concentration to one drop of 7 per cent tincture of iodine to a quart of water and allowing it to stand 30 minutes. He states that all harmful bacteria are killed and that the amount of iodine is too slight to taste.

Turrentine (174) advocates the use of sea-weed for the prevention of goiter. He has prepared tablets of the sea-weed *Macrosystis pyrifera* for prophylactic purposes. Jarvis, Clough and Clarke advocate the use of salmon for the purpose of prophylaxis, and state that the eatable portions of the body rich in fat are highest in iodine content. According to their analyses the prophylactic dose would be not less than 3 ounces per person per day, of the variety showing the lowest iodine content, and this would not be sufficient total iodine intake but merely a supplement to that from other natural sources.

It is not the purpose of this paper to discuss the pathology of the thyroid or methods of therapeutics, but only the distribution of iodine from a quantitative standpoint. It seems in order, however, to point out that many statements in the literature tend to mislead the reader in regard to quantities of iodine used. After a careful review of the literature on the pathology and therapeutics of the thyroid, it seems evident that high iodine intake can be shown to have nothing to do with the origin of any form of goiter (175). Statistics indicate that low iodine intake is correlated both with simple goiter and exophthalmic goiter. The classification of adenomatous goiter is not usually available in statistics and very probably there is no easy way to distinguish between toxic and non-toxic adenomatous goiter. If we admit the existence of a subdivision of adenomatous goiters (toxic) consisting of thyroid which are capable of producing an abnormally large amount of thyroxin if iodine is available, then the feeding of large amounts of iodine might be of diagnostic significance, in that this would enable the gland to produce a large amount of thyroxin and the thyroxin would raise the basal metabolism and thus lead to diagnosis of toxic adenoma. If on the other hand, a deficiency of iodine was present with the ability of the thyroid to produce too much thyroxin, the diagnosis of toxic adenoma would not be possible. In communication with physicians who are careful in the determination of basal metabolism on these cases at frequent enough intervals to adequately study their history, it appears that in cases of toxic adenoma a large dose of iodine will produce hyperthyroid-

ism, but apparently the iodine which is not made into thyroxin is excreted and the iodine from the destroyed thyroxin is also to a large extent excreted so that at the end of about a month the metabolism may be down to normal. In other words the effect of the iodine is about the same as the effect of a single over-dose of thyroxin. Therefore, it seems evident that iodine is of only diagnostic importance in this case and leads the physician to recommend thyroidectomy. If this iodine was not taken intentionally the patient would nevertheless be always in danger of hyperthyroidism due to the *unintentional* taking of large doses of iodine in the form of oysters, shrimps, crabs, lobsters, cough-medicine, or in other ways. Since heavy doses of iodine (usually 10 drops of Lugol's solution per day) are given to patients for a number of days before exophthalmic goiter operations, and small doses of iodine are recommended by physicians after various goiter operations, it seems inconsistent for physicians to say that these doses of iodine are harmful. The quantity of iodine necessary to produce a rash on the skin is very much larger than the doses ordinarily employed in goiter prophylaxis and inconvenience from that point is unnecessary. It seems evident, therefore, that most of the statements concerning the harmfulness of iodine are exaggerations. The taking of large enough doses of iodides to produce a rash on the skin and of elementary iodine (I_2) to cause an inflammation of the mucous membranes, is so rare as to be entirely ignored nowadays, although it occurred perhaps more commonly in the past century.

XV. Methods of iodine analysis. It would require too much space to refer to the original papers on iodine analysis. Some references are given in the beginning of this paper and only a few recent references will be given in this section.

If sufficient iodide is present for weighing, it may be precipitated as palladous iodide (PdI_2) by the addition of palladous chloride to the acid solution. After standing two days in a warm place the precipitate will be coarse enough to filter through a Gooch crucible. Wash with warm water, dry at 100° and weigh. Stieglitz (176) uses this reaction for microchemical detection of iodine in tissues. Usually the sample is too small for a gravimetric determination and the iodide is oxidized to iodine and determined by titration or colorimetrically.

Titration (Fordos and Gélis, 1842) is usually done with standard sodium thiosulfate solution (in acid or neutral solution) and the reaction may be written as follows: $2Na_2S_2O_3 + I_2 = 2NaI + Na_2S_4O_6$ (sodium tetrathionate). In alkaline solution some sulfate is formed.

Colliodal solution of starch is used as an indicator. Although the composition of iodized starch is in dispute, the reaction is more sensitive if one I^- (as well as I_2) is present. (On prolonged heating of the solution the starch reduces the iodine and the presence of an oxidizing agent is necessary to restore the color.) Obviously the titration is not quantitative if other oxidizing substances are present in addition to I_2.

The oxidation of iodide to iodine must be done without oxidation of iodine to iodate or ICl and the most useful oxidizing agent is nitrous acid.

According to Lewis and Randall (177, page 599)

$$I^- + NO_2^- + 2H^+ = \tfrac{1}{2}I_2 \text{ (solid)} + NO \text{ (gas)} + H_2O \text{ (liquid)} \qquad (1)$$

$$\frac{(NO)}{(I^-)\ (NO_2^-)\ (H^+)^2} = 10^{10}$$

Since there would be half as many iodine molecules as NO molecules the production of NO would be a measure of the yield of I_2 and the percentage yield would be greater the greater the concentrations of NO_2^- and H^+.

There is the possibility of the following side reactions:

$$NO_2^- + I_2 \text{ (solid)} + H_2O \text{ (liquid)} = NO_3^- + 2H^+ + 2I^- \qquad (2)$$

$$\frac{(NO_3^-)\ (H^+)^2\ (I^-)^2}{(NO_2^-)} = 10^{-10}$$

The production of NO_3^- would be a measure of I_2 reduced but this could be made small by the increase in (H^+).

The nitrous acid will decompose as follows:

$$3NO_2^- + 2H^+ = NO_3^- + 2NO \text{ (gas)} + H_2O \text{ (liquid)} \qquad (3)$$

$$\frac{(NO_3^-)\ (NO)}{(NO_2^-)\ (H^+)} = 10^{11}$$

This reaction may be retarded by preventing the escape of NO and by reduction of (H^+) or presence of O_2 (178).

$$4NO + O_2 + 2H_2O = 4HNO_2 \qquad (4)$$

$$NO_2^- + 3I^- + 4H^+ = \tfrac{1}{2}\ N_2 + 3/2\ I_2 \text{ (solid)} + 2H_2O \text{ (liquid)} \qquad (5)$$

This reaction occurs so slowly that it may be neglected.

Owing to the decomposition of nitrous acid (3) it is not useful as an oxidizing agent where the iodine is to be distilled off.

Kurtenacher (179) studied the reaction

$$IO_3^- + 3HNO_2 = 3NO_3^- + I^- + 3H^+ \quad (6)$$

in a solution of $KHSO_4$. It might be of importance in the presence of a mixture of iodide and iodate.

Iodate may be more rapidly reduced to iodide by the action of sulfurous acid. According to Macaulay (180) there may be an intermediate formation of yellow SO_2HI but the final result is quantitative (stoichiometric). Loss of SO_2 by oxidation by the air is negligible.

If a solution of iodine is made alkaline, hypoiodite is formed which quickly changes to iodate. The rate of the reaction has been studied by Lievin (181).

$$I_2 + 2KOH = KI + KIO + H_2O \quad (7)$$

$$3KOI = 2KI + KIO_3 \quad (8)$$

Combining 5 and 6 we have:

$$3I_2 + 6KOH = 5KI + KIO_3 \quad (9)$$

The above reaction is reversed by making the solution acid and is the basis of a micro-method for the determination of iodine in which the iodine is oxidized to iodate in acid solution; the excess of the oxidizing agent is removed and an excess of KI is added. The iodine produced is six times the quantity of the original iodine so this makes possible the determination on a sample one-sixth the ordinary size. The difficulty of this procedure lies in the complete removal of all oxidizing agents. Since atmospheric oxygen is difficult to remove and since the rate of oxidation by atmospheric oxygen is very slow except in the presence of catalysts such as iron and manganese, chemists are usually content with the removal of these catalysts, rather than the removal of oxygen. Since the phosphates of heavy metals are soluble to an almost immeasurably extent, it is well to use phosphoric acid as an acidifying agent and if any precipitate is formed, filtering it off before adding KI. After completion of the titration of the iodine formed, by means of thiosulfate, if the solution is allowed to stand, iodine is slowly liberated by the action of the oxygen of the air. The rate of this reaction will demonstrate the activity of catalysts that the chemist has not succeeded in removing and give him an idea of the magnitude of a possible error from this source.

The oxidation of iodide or iodine in strong HCl solution may lead to the formation of ICl (182). The oxidation never proceeds further than this even with the strongest oxidation agents. Some of these agents

are HIO_3, $HClO_3$, Cl_2, HOCl permanganate and salts of manganese. If the solution is shaken with an organic solvent immiscible with water, the ICl may pass into this second phase and give a color which is different from that of iodine and may be similar to bromine. In the water solution ICl is bright yellow in color. If the HCl concentration is reduced very much the ICl is dissociated by hydrolysis giving rise to iodate. By the reduction of iodate with iodide in the presence of HCl, I_2 is formed if there is an excess of iodide, but if there are less than two molecules of KI for one of HIO_3, ICl is formed.

In the colorimetric determination of iodine it is most conveniently dissolved in carbon tetrachloride. In this the iodine has a violet color similar to iodine vapor and the spectrum shows a dark band in the green in the region where most of the strongest lines of the line spectrum of iodine vapor occur. In water, iodine has a brown color and the spectrum shows the same band but shows more absorption at the violet end which is supposed to be due to combination with the solvent. Some solutions of iodine are red and the red color is supposed to be due to a mixture of the violet and the brown. Very dilute solutions in carbon tetrachloride appear pink. (ICl in vapor and water solution has a color similar to bromine but is said to be red in carbon tetrachloride.) If a water solution of iodine is shaken with an equal volume of carbon tetrachloride, about $\frac{85}{86}$ of the iodine passes into CCl_4. If neutral salts are added to the water phase they reduce or increase the solubility of iodine in the water, whereas the solubility in CCl_4 remains constant. In the analysis of iodine by this extraction method either a sufficiently correct estimate of the partition coefficient is made and care taken that equilibrium is reached, or else the total iodine is removed by repeated extractions.

The effect of neutral salts on the partition of iodine between carbon tetrachloride and water is shown in the following table, as calculated from their solubilities (182) at 25°. The partition coefficient is the concentration in CCl_4 divided by the concentration in H_2O at 25°. Normal solutions of salts are used:

Normal solutions	*Partition coefficient* $\frac{CCl_4}{H_2O}$		*Partition coefficient* $\frac{CCl_4}{H_2O}$
Na_2SO_4	189.6	$NH_4C_2H_3O_2$	68.9
K_2SO_4	127.5	NaCl	52.8
$(NH)_2SO_4$	123.3	KCl	46.2
$NaNO_3$	118.1	NH_4Cl	41.3
KNO_3	114.1	NaBr	9.22
Pure water	89.3	KBr	7.98
NH_4NO_3	80.9	NH_4Br	7.58
		KI	2.52

According to Jakowkim (183) the molecular weight of iodine in CCl_4 changes with the concentration of iodine so that the partition coefficient changes with concentration. At saturation, the partition coefficient is the ratio of solubility in the two solvents. The partition coefficient between CCl_4 and pure water, decreases with decreasing concentration of iodine. Herz (184) extrapolated it to infinite dilution and obtained the value of about 85, although at saturation it was 89.3. It seems probable that all the partition coefficients in the above table would be decreased slightly with dilution of the iodine. Ignorance of the salt concentration of the water phase would cause an error in the analysis of iodine which would be greater the greater the volume of the water phase in relation to the CCl_4 phase. In the presence of much bromide or iodide accurate results could evidently not be obtained. If the volume of the two phases are equal (assuming saturation with iodine) there would be $\frac{1}{89}$ as much iodine in the water as in the CCl_4, in a normal solution of Na_2SO_4 there would be $\frac{1}{190}$ and in a normal solution of NH_4Cl, there would be $\frac{1}{41}$. If no Br^- or I^- were present and the other salts were disregarded and it were assumed that there was $\frac{1}{89}$ in the water phase, the error due to presence of unknown salts would be less than 1 per cent. In general, it may be stated that chlorides are to be avoided since they decrease the extraction by CCl_4. Their action may be antagonized by sulfates and nitrates.

In the presence of large amounts of salts, the water phase would have to be very large to keep them in solution. It is best to remove them. This can be done simply by crystallizing them out by evaporation of the solution, or by precipitation with alcohol. When alcohol is added either two or three phases may be produced. If three phases are produced, 1 is the crystallized salt, 2 is the water-and-salt-rich, alcohol-poor phase, 3 is the alcohol-rich, water-and-salt-poor phase. With small amounts of iodide there should be none in phase 1, but it remains to be demonstrated how iodine is distributed between phases 2 and 3. If the volume of phase 3 is much larger than phase 2, it is probable that phase 3 will contain most of the iodide. The rest of the iodide may be removed from phase 2 by repeated extraction with alcohol. Sometimes the volume of phase 2 is so small that it merely forms a film over the surface of the crystals and sticks them together into a pasty mass which cannot be washed easily with alcohol. This may be avoided by Von Fellenberg's method of adding potassium carbonate solution which will

go entirely into phase 2 and increase its volume. This results, however, in a more voluminous liquid phase to be extracted with the alcohol. Another method is to evaporate the solution to complete dryness, powder it, and extract it with absolute alcohol, in which case only two phases are present (salt crystals and alcoholic solution). Since KI is soluble in alcohol to the extent of about 14 per cent, and KCI only very slightly soluble, this is a very effective way of separating the iodides from other salts.

In the presence of organic matter, this has to be burned before the iodine is completely liberated. Some chemists merely char the material but it is well known that iodine is adsorbed by charcoal and, furthermore, the charcoal may occlude iodine. In the manufacture of activated charcoal it is found that in order to eliminate organic compounds a white heat is necessary. Since it is not possible to heat up materials to a white heat without loss of iodine, the charcoal probably always contains organic compounds, which are partly tarry substances and may be combined with iodine. In the burning or distillation of coal and wood, it is well known that a large amount of iodine is found in the soot or tar, and in the burning of material for iodine analysis it is necessary to prevent iodine from escaping in this way. In the burning of sea-weed for the extraction of iodine, at least 33 per cent of the iodine is lost, according to Lapique (185), although the sea-weed has a very alkaline ash, containing about 50 per cent of potassium carbonate. This loss of iodine is inhibited by the addition of alkali solution to the material before it is ashed or by fusing it with KOH or NaOH. A still better method, according to Von Fellenberg, is the use of alcoholic KOH to wet the material or digest it before ashing. It seems that sodium ethylate might be useful for this purpose.

When large amounts of organic matter are present, large amounts of alkali are necessary in order to prevent loss of iodine and great difficulties arise in the complete combustion of all carbon. If the ash fuses at the temperature of the combustion it coats-over particles of carbon and thus prevents oxygen from reaching them. Two methods to avoid this have been used. One is to add sufficient $CaCO_3$ to the material so that the ash will not fuse. The other is to char and extract the charcoal with water, then filter and burn the charcoal separately. But when this is done it is found that some organic matter usually passes into the filtrate and necessitates the burning of the residue of the water extract, which

will fuse and cause the same difficulty again. This has been obviated by adding KNO_3 to the fusion. This addition is liable to cause small explosions with loss of iodine and should be added in milligram portions. If the fusion mixture is largerly caustic alkali, it is probable that no iodine is lost by the oxidative action of the nitrate, but if the fusion is due largely to chlorides or phosphates, it seems probable that iodine would be lost in this way. In order to avoid these difficulties the material may be burned in a combustion tube and the burned products led through a KOH solution for the absorption of iodine (McClendon, 186). In this process there are sometimes particles of smoke formed which are not caught by the alkaline solution. These smoke particles are electrically charged and repel one another so that they are dispersed in the entire space in which they are contained, and those in the middle of a gas bubble do not get close enough to the solution to be caught. In fact it is found that if powdered P_2O_5 is blown into air that is passed through a wash bottle, not all of it is caught in the water. In order to catch all the smoke particles a small Cottrel-precipitator was used by the author (187). In this case the material from the precipitator and the alkaline solution had to be collected and burned again in a tube.

This completes the principles of the methods that have been used, but a few practical hints from recent micro-methods will be given. Winkler (188) in the determination of iodine in sea water placed 1 litre of sea water in a separatory funnel and added 10 cc. concentrated HCl and 5 cc. of 0.01N arsenic trioxide (0.5 cc. of 0.1N sulfurous acid may be substituted) to reduce iodate. Fifty cubic centimeters of CCl_4 and 5 cc. of 1 per cent $NaNO_2$ were added and the funnel shaken. The extraction was repeated twice. Each 50 cc. of CCl_4 extract was received in a 100 cc. separatory funnel in succession and extracted with the same 10 cc. of water containing five drops of 0.1 per cent sulfurous acid. Owing to the reducing action of sulfurous acid on the iodine it was all changed to iodide, and since iodide is not soluble in CCl_4 it could all be shaken out into the water. This water extract was treated with 5 drops of nitrite and 10 drops of 10 per cent H_2SO_4, and extracted three times with 5 cc. portions of CCl_4. These 5 cc. portions were successively extracted in a 10 cc. separatory funnel with 1 cc. of H_2O to which two drops of sulfurous acid had been added. This water extract was then treated with two drops of nitrite and 5 drops of H_2SO_4 and extracted with $\frac{1}{4}$ cc. of CCl_4. The iodine now was sufficiently concentrated to be colored pink. It was then run into a very small glass stoppered bottle. By making up artificial sea-water samples containing known quantities

of iodine and treating them in the same way, a series of comparison bottles was made for estimating the unknown colorimetrically. In this way it was found that seawater contained 0.035 mgm. of iodine per litre. This method has been used by the author and it is very satisfactory if the sea-water is free from organic matter. Organic matter causes foaming in the separatory funnel. The foam may be broken with a glass rod or by using a special carrier in the centrifuge to rotate the separatory funnel (International Instrument Company), but it is difficult to prevent leakage of the stopcock of the separatory funnel in the centrifuge, and although the foam is broken, some iodine may be held back by the organic matter.

Technical CCl_4 contains reducing substances which must be removed before it is used for extracting iodine quantitatively. This is done by adding bromine (or chlorine), letting stand in an ordinary glass vessel in a sunny window for a week, washing with NaOH solution and then with tap water and distilled water, filtering-out all the water possible with ordinary filter paper, filtering through a layer of plaster of Paris to remove water that has passed the filter, and distilling. The first part of the distillate is cloudy (possibly with water droplets) and is rejected. Distillation may be continued so long as a thermometer in the vapor does not show a temperature above 76°.

All reagents should be tested to show that the quantity used in an analysis does not contain enough iodine to vitiate the results. Reagents may be purified by recrystallization from water or alcohol.

Neither sea water nor any other material so high in chlorides and low in iodide can be conveniently subjected to ordinary methods for combustion of organic matter without loss of iodine. It was observed (189) that iodine was not recovered quantitatively after merely charring organic matter. Therefore, the author's method of combustion in a tube has been applied to various classes of materials. The tubes have been made of various sizes, but since one end may be left open and material fed into it during combustion, tubes of two sizes will suffice. Pyrex tubes may be used repeatedly if care be taken against overheating and no ash be allowed to fuse with the glass. Fused silica tubes are heat-resistant but if ash be allowed to fuse with the silica, thin silica tubes crack on cooling or reheating about as easily as pyrex tubes. If ash fuses on thick opaque silica the ash may be lost spontaneously by chipping off of the surface of the silica, but this makes the tube thinner and repetition of the process will finally lead to fracture. If all of the glass formed by fusion of the silica with ash is removed with HF solu-

tion, the tube will last longer, as the HF removes less silica than would otherwise be lost in chipping. Broken tubes may be repaired in the oxy-gas flame but it is not worth while repairing them unless the silica is free from bases (ash).

The apparatus consists mainly of a silica tube two feet long and three and one-half inches bore with an elbow one foot long and one inch bore. The material to be burned is placed on a clean sheet of iron bent to fit the tube. A new sheet of iron may be used for each determination. Several kilograms of material may be burned by adding portions during the combustion. Oils to be analyzed are fed in through a small tube. Oxygen from a reducing valve is sprayed by means of a glass nozzle into the open end of the tube, care being taken not to blow the ash off of the iron sheet. No heat is applied to the outside of the tube so long as the material will burn of its own accord after lighting it with a match. The elbow passes down into a pyrex absorption flask containing very dilute NaOH solution. Two constrictions on the flask prevent spray from being carried out of the side-neck that leads to the Cottrell precipitator. The main opening of the absorption flask is almost closed by the introduction of the elbow, the crack being plugged with moist asbestos fibres.

In order to reduce convection currents the open end of the large silica tube is partially closed with a disc of sheet iron having a slit in it for the oxygen nozzle. This disc may be removed when adding portions of the sample.

The Cottrell precipitator consists of three lead-glass tubes, 1 inch bore and 3 feet long with a one-half inch side-neck near each end. The three tubes are connected in parallel by means of these side-necks. The tubes are covered with tinfoil and the ends are closed with rubber stoppers through the center of each of which runs a fine nichrome wire. One of the secondary terminals of a Ford spark coil is connected to the nichrome wires and the other to the tinfoil coverings. The side-necks of one end of the precipitator are connected with the absorption flask and those of the other end with a rotary suction pump. The more rapid the suction is the hotter the fire will be and the less the danger of soot or tar production, but it should be slow enough to permit complete precipitation of the smoke. It is, therefore, adjusted to the maximum speed permitting complete precipitation and the quantity of material added at one time is made small enough so that no soot or tar is formed.

The ash, NaOH solution, nichrome wires and rinsings of the apparatus are collected, evaporated to dryness and burned in a smaller tube, 2

inches bore, 1 foot long, and with elbow $\frac{1}{2}$ inch bore and 8 inches long. A smaller absorption flask is made to fit it and no precipitator is used. A filter pump will furnish enough suction. The combustion is performed in the same way, except that external heat must be supplied from the start and greater care taken that the oxygen does not blow the ash away. The oxygen nozzle may be expanded to equal the diameter of the tube. A multiple Bunsen burner or large fish-tail burner, may be used with the air cut down until the flame begins to be luminous. Care should be taken that no soot from the flame is sucked into the tube.

Some method should be used for reduction of the salt content of the combined ash and NaOH solution. In case the bulk of the material is large it is advisable to extract it with alcohol. A ball-mill is useful for this purpose. The extract (or mother liquor) containing the iodine is evaporated to dryness and gently heated to verify the complete combustion of the organic matter. It is dissolved in 5 cc. H_2O, 1 drop of 0.1N sulfurous acid added and the solution neutralized with phosphoric acid (using test paper made by drying an alcoholic solution of bromphenol-blue or methyl orange on acid-washed filter paper) and allowed to stand 2 minutes. Most of the CO_2 and SO_2 is boiled off and the solution cooled. If a precipitate forms, filter. The volume is made up to 10 cc. in a 12 cc. separatory funnel. One cc. of purified CCl_4 and about 5 mgm. of $NaNO_2$ are added and the separatory shaken 2 minutes. The CCl_4 is run into a 1 cc. glass stoppered bottle and centrifuged to remove water droplets. The CCl is run into the left hand cup of a micro-colorimeter of Duboscq type (Bausch and Lomb) and set at 20 mm. In the right hand cup is placed CCl_4 containing 0.1 mgm. of iodine per cc. After a color match is made, the reading of the standard in mm. divided by 200 will give the milligram iodine in the CCl_4. Since 10 parts remained in the aqueous phase and 85 parts were in the CCl_4, the latter contains $\frac{85}{95}$ of the total. By multiplying the milligrams in the CCl_4 by 1.118, the total milligrams may be calculated.

Space does not permit us to describe any exact details of procedure but this method is adapted for large samples low in iodine. In the case of drinking water, 100 liters are evaporated down and filtered when the volume of about 1 liter is reached. Further filtration should not be performed until the organic matter is burned. It is evaporated to dryness and burned in the small tube. Fusion with alkali would be simpler but usually the residue, when it is evaporated to dryness, is rather bulky, and fusion with alkali is attended with difficulties, so that it is better to burn it in the small tube.

Cereals have so little iodine in them that several kilograms may be required, but they burn very easily in the large tube by the addition of small amounts at a time during the combustion.

Oil volatilizes so rapidly that complete combustion cannot be obtained unless it is sprayed in through a fine opening during the combustion.

Soils may be burned in the small tube and extracted with HCl containing sulfurous acid. The soluble iodide may be determined in this extract. The insoluble portion should be ground to a powder and fused with NaOH in order to dissolve the silicates.

In burning any material containing phosphates such as dried urine, which will fuse and occlude carbon particles, this fusion may be prevented by mixing with $CaCO_3$ before burning in the tube. Sometimes the iodine in CCl_4 is contaminated with bromine or some other yellow substance so that a colorimetric reading can not be made. In this case it is usually possible to remove the extraneous coloring matter by placing the CCl_4 in a small separatory funnel, adding 1 cc. of water, plus 0.01 cc. of 0.1N sulfurous acid, shaking two minutes, draining out the CCl_4, adding 1 cc. of fresh CCl_4 and 0.01 cc. of nitrosyl-sulfuric acid, $OH \cdot SO_2 \cdot ONO$ and shaking 2 minutes. In this case it should be remembered that $\frac{1}{8}\frac{1}{6}$ of the iodine remains in the water.

Von Fellenberg (190), in order to avoid combustion in a tube, reduces the size of his colorimeter and uses so small a sample that it may be burned in an open crucible with alkali. He evaporates the water sample to dryness, adds KOH solution and evaporates again, then burns in an iron or platinum dish, moistens it with a few drops of concentrated potassium carbonate solution and grinds with 95 per cent alcohol with an agate pestle, decants the alcohol, then repeats the process by rubbing with a few cubic centimeters of alcohol 4 times. The combined alcohol is diluted with water plus 3 drops of potassium carbonate solution and evaporated in a platinum dish on the water bath. The residue is ignited gently, moistened with potassium carbonate solution, extracted with alcohol, and evaporated again and heated until the bottom glows for an instant only and the flame is withdrawn. Three-tenths cubic centimeter of water is added and the water extract is run into a narrow glass tube, 5 mm. bore and 8 mm. high. The water remaining in the dish is determined by weighing and account taken of the iodine lost in this way; 0.01 cc. of chloroform is added and a drop of a solution of about 50 mgm. of $NaNO_2$ in 10 cc. of 3N H_2SO_4 is added, is then shaken one-hundred times and placed in the centrifuge and compared with tubes of the same

bore in which known quantities of KI have been analyzed in the same way. The unknown tube is matched with a known tube by means of a magnifying glass.

For iodized salt, 100 grams are dissolved in 300 cc. of water plus a little bisulphite, and acidified with HCl, then made alkaline to phenolphthalein and evaporated until considerable salt has crystallized out. Twenty cubic centimeters of concentrated potassium carbonate solution are added and 50 cc. of alcohol, and the mass shaken. The upper layer is removed and the process repeated three times. The combined alcohol extracts are evaporated after addition of $\frac{1}{2}$ cc. of potassium carbonate solution until the salt begins to crystallize and extracted three times with a few cubic centimeters of alcohol. The alcohol extract is placed in a platinum dish, water added and evaporated after adding 10 drops of potassium carbonate solution. The residue is ground with a few cubic centimeters of alcohol and a few drops of potassium carbonate solution. The alcohol is evaporated after adding two drops of potassium carbonate solution, gently ignited and analyzed as described above.

Soils and rock are extracted with HCl. Two grams of HCl-soluble material are used for analysis. A one to one solution containing 2 grams of sulfite per liter of HCl is added in small portions until CO_2 ceases to be evolved, foaming is controlled with a drop of ether. The solution is diluted and centrifuged, made alkaline to phenolphthalein, and 5 cc. of potassium carbonate solution are added. It is evaporated until crystals form, 40 cc. of alcohol added, and the upper layer removed. This is repeated three times and the combined alcohol extracts are evaporated and analyzed as described above.

Two grams of the HCl-insoluble portion and 6 grams of KOH and a little water are heated in an open iron dish, carefully fused and cooled, a few cubic centimeters of water are added and carefully heated until the whole mass has absorbed the water and the whole is thrown into a vessel with water, and the dish washed out repeatedly with water. HCl (containing sulfurous acid) is used to neutralize this, with phenolphthalein as indicator.

With plant and animal material the iodine content must be known in a general way in order to choose the size of the sample (from 10 to 50 grams of dry substance). To this is added 25 per cent of its weight of KOH. Alcoholic KOH penetrates better and saponifies the fats, thus preventing loss of iodine in the volatilization of organic materials. The material is burned to a char, extracted three times with water, and filtered. The char is burned again, the water extract added and evapo-

rated and gently ignited, and is ready to analyze as described above. Urine may be diluted with $\frac{1}{10}$ of its volume of concentrated potassium carbonate solution, evaporated and ignited.

The extraction of ash with alcohol, as performed by Von Fellenberg, is very laborious and it seems unnecessary to apply it to iodized salt. The iodide may be extracted from the dry salt with absolute alcohol. Winkler (191) extracts iodized salt with alcohol.

Kendall (192) has had a great deal of experience with the titration method for the determination of iodine where relatively small samples of animal tissue are necessary. About $\frac{1}{2}$ gram of the dried material (thyroid) is fused in a nickel crucible with 10 grams of NaOH after thoroughly wetting the material with a few drops of NaOH solution. A little lactose is added to prevent spattering. The fusion is carried out in a crucible furnace to prevent overheating. Oxidation is completed by adding KNO_3, 5 mgm. at a time until no more bubbles appear on addition. The fused mass is poured out and the crucible cooled, and dissolved in 200 cc. of water; $\frac{1}{2}$ cc. of 20 per cent $NaHSO_3$ and 2 drops of methyl orange added, and neutralized with phosphoric acid, after which 5 cc. of 20 per cent phosphoric acid and a lump of hard coal are added, volume made up to 250 cc. and boiled 10 minutes or longer until the volume is 200 cc. It is cooled and bromine added until it is yellow, boiled until colorless, and 5 minutes longer. This oxidizes the iodide to iodate. The coal is removed and a few crystals of salicylic acid added to destroy traces of bromine. The solution is cooled and 5 cc. of 20 per cent phosphoric acid that has been boiled with aluminum strips added; 1 gram of KI is added and it is titrated with 0.005 N thiosulfate.

CONCLUSIONS

Extensive data are given to show that iodine is of very wide distribution as minute traces and is more or less concentrated by the leaves of plants and the thyroid glands of animals. Goiter is due to a deficiency of iodine. Since the clinical literature cannot be reviewed, the following conclusions from the latest paper by Kimball (193) are quoted:

> Every survey or study only emphasizes the importance of prevention during pregnancy. The relation of these congenital defects to the adenomatous or tumor conditions of later life is being appreciated more and more with each careful study. Also we all know the disappointments in our attempts to control or treat these tumorous thyroids. Therefore, we cannot stress this point too strongly and in endemic goiter districts we need the attention of the physicians

who educate and direct women through this important period, and of every prospective mother. It is during pregnancy that the general use of iodized salt will be of greatest value and should be used in every case unless otherwise directed by a physician.

The history of this problem for the past century teaches most emphatically that the treatment of goiter is very unsatisfactory and accomplishes very little toward the control of the disease, but those attacking the problem from the viewpoint of preventive medicine—physiologists, biochemists and public health authorities—have accumulated sufficient evidence to justify the assertion that endemic goiter is the easiest known disease to prevent. By further detailed study of the fundamental principles underlying the cause and prevention and with the constant application of scientific data by the state health organizations, we should see the fulfillment of our earlier prediction: Within another generation there will be no endemic goiter problem.

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THE QUESTION OF CARDIAC TONUS

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The volume of literature on most scientific subjects is inversely proportional to the facts known. This is a healthy condition for it shows many are attempting to clear the field. Cardiac tonus, however, offers an exception to our general rule, for aside from the earlier papers having to do with the tortoise auricle, very few have appeared in recent years dealing with this subject alone. Most of the references and experiments having to do with the tonus of cardiac musculature have been buried in articles often bearing titles but little suggestive of the task at hand.

Few things can probably be more rash than the review of a subject, the very definition of which is a matter of question. The tonus of skeletal muscle has been defined by Cobb (19) as "That state of constant muscular tension which underlies and makes possible all orderly motion." Evans (21) says "The tonus of muscle may be defined as a resistance of its substance to extension." This is similar to Henderson's statement (44) that tonus is "The degree of resistance to deformation." Patterson, Piper and Starling (66), believing that diastolic ventricular tension changed but little or not at all with moderate increases of inflow, have given up the conventional ideas of tonus entirely and have defined cardiac tonus as the "physiological condition or fitness of the muscle fiber, and its measure is the energy set free per unit length of muscle fiber." Bordet (9) takes the same point of view as Starling believing that the power of opposing dilatation is not in diastole but in systole. He would replace tonus with the term "energy of contraction." Wiggers (87) looks upon tonus as "A sort of a sustained partial contraction of muscle tissue by virtue of which the muscle fibers resist stretching more than they would by virtue of the inherent elasticity alone."

It is evident from these definitions that the word tonus has at times included in its meaning such diverse things as the elastic properties of muscle, the physiological fitness of its fibers, and a sustained degree of contractile activity. The word has, however, been used still more loosely. To many physiologists and the majority of clinicians any form

of cardiac dilatation is an example of low tonus, and conversely if the diastolic size is reduced, the tonus is said to be correspondingly high. Such a conception is of course neither accurate nor clear, for it ignores the facts that the diastolic size of the heart may be determined by the pressure and amount of blood entering from the veins, and that dilatation may be a physiological compensating mechanism. The word tonus has been used frequently enough, but seldom can it be clearly seen with just what limitations, and phenomena of very different biological values have often been designated with its name. It is small wonder then that some writers urge abandoning the word tonus and substituting such harmless phrases as "extensibility," "power of relaxation," or "changed condition of the course of contraction" until our ideas on the subject become clarified.

In order to discuss cardiac tonus it is necessary however to formulate some kind of a conception of the meaning of the term, even if this be arbitrary and incomplete. The word tonus in physiology has come to mean continuous activity of a slight degree. For our purpose we shall say that cardiac tonus is a sustained partial contraction, independent of the systolic contractions, by virtue of which the muscle fibers resist distention during diastole more than they would because of their mere physical properties. This is practically Wiggers' definition with the addition of a phase to exclude phenomena dependent on the course of the rhythmical contractions. To say that tonus is the resistance of the heart muscle to stretching in diastole, as many writers have done, is entirely too comprehensive for it would include such diverse things as sustained diastolic contraction, contraction remainders, contractures and the inherent elasticity of the muscle. The purpose of this review is not to pass on the exact nature of tonus but to examine the evidence whether or not an active tonus exists that can be modified to meet varying physiological conditions.

The demonstration by Brondgeest of skeletal muscle tonus dependent on nerve connections, together with the undoubted tonicity of the smooth muscle in the vascular system to which the heart musculature is closely related, led the early workers to accept the idea of cardiac tonus without much question. Even Gaskell (33) quite aware of the difficulties in the situation still included tonus in the sense of a sustained contraction during diastole as one of the fundamental properties of cardiac muscle and believed it to be under nervous control. Studies on the auricle of the cold-blooded forms quite confirmed these views. In recent years, however, physiological authorities have been much more

conservative in their statements regarding the existence of cardiac tonus and the majority certainly would at least agree with Wiggers (87) when he says that convincing experimental evidence has not yet been presented that tonus of the mammalian ventricle is capable of changing under conditions that may be considered physiological.

What function could ventricular tonus have, is a question well worth asking. In skeletal muscle it is apparent that tonus is a mechanism by which the contraction may be made more prompt and precise and by which posture may be maintained. There is nothing quite comparable to this in the beat of the heart. Tonus means a certain resistance to be overcome during each diastole, at first sight clearly wasted effort. There are two or three possible advantages, however. The clinicians have always believed that a certain degree of contraction was necessary during diastole to prevent any incompetence at the valvular orifices. In the case of lesions, low tonicity might transform a small mitral leak into a large one, and high tonicity might greatly improve the condition. If we assume that the systolic discharge is related to tension, a controversial point in cardiodynamics for which however there is much evidence, tonus may of course function in determining the initial intraventricular pressure. In the third place, tonus might protect against too great dilatation and any resulting injury.

There may be said to be two absolute tests for the existence of cardiac tonus. The first of these is a spontaneous change in the extent of diastolic relaxation where all other factors are held constant. The second is the necessity of varying some physiological condition which does not involve a change in the contour of the rhythmical contraction, in order to secure the preceding degree of relaxation. The physiological factors which must be held constant, or one of which may be varied within normal limits, are temperature, CO_2 and O_2 content, the influence of nerves, the distending pressures, and the chemical composition of the nutrient media. Changes in relaxation may be due to indirect influences which come from variations in rate, the extent of contraction, the duration of the phases of the cardiac cycle, particularly the diastole, and these must be carefully excluded. The difficulty of controlling many of these factors in a quiescent tissue is great enough but the difficulties are multiplied when we deal with an automatic rhythmical organ such as the heart. It is for this reason that the literature is full of references to variations in diastolic length of the ventricle, few of which can be unquestionably related to tonus.

In practical experimental studies of tonus one must depend on curves

by suspension methods, volume curves from plethysmographs, and intra-auricular and intraventricular pressure curves from the various types of manometers. If tonus be looked upon as resistance to distention then it should vary directly as the volume-elasticity coefficient of the relaxed heart (Wiggers), that is, the ratio of the pressure increase to the volume increase. If the heart were distended by equal increments of pressure and the volumes determined for each increment, then pressure might be plotted against volume and a curve obtained which could be called a tonus curve. If the procedure were repeated after varying some factor, say vagal stimulation, a comparison of the two curves would readily indicate any change in tonus. A given pressure would cause a greater volume change when tonus was low. It is evident from this reasoning that dilatation would not be evidence of a change in tonus unless the pressure-volume ratio were abnormal.

Tonus of the cold-blooded auricle. In the year 1887 (23) Fano discovered and described tonus waves in the atrial musculature of the tortoise Emys europaea. The fundamental contractions, the rhythmical systoles, were often superimposed on other slow spontaneous contractions of a much slower tempo, the tone waves. The two types of waves were found to vary independently of each other, a rise of temperature for example increasing the former and abolishing the latter. Tone waves appeared in the tips of the auricles in which no ganglia were found. Fano believed that the tone waves were myogenic in origin and that there were probably two kinds of muscular elements in the atria. The waves were seldom seen in the ventricle.

In succeeding papers Fano and his associates (24, 25, 26) presented many more interesting characteristics of these auricular tonus waves. Stimulation of the vagus never inhibited them, but left them either uninfluenced or often increased. Muscarin was found to be a stimulant and atropin, nicotine and veratrine depressants. On Schmiedeberg's assumption that digitalis affected the elastic rather than the contractile properties of muscle, Fano and Sciolla (24) studied the action of this drug on the tonus waves. It was found to abolish them along with the regular contractions although at the same time it greatly increased the general tone level. From this it was argued that the functional oscillations of tonus had to do with the property of contractility and not elasticity. The question of electrical variations during the tonus waves was investigated by Fano and Fayod (25) who found by means of the capillary electrometer that the auricle gave an electrical tonus in which the same oscillations could be observed as in functional tonus. The

oscillations could be provoked by vagus stimulation. Reasoning from the Gaskell (33) phenomenon of increased postivity during vagal action, Fano and Fayod felt that the tonus oscillations indicated periodic augmentation of the nutritive processes.

Studies on auricular tonus, particularly in the Batrachian heart, were continued by Bottazzi. He believed that the tonus oscillations were independent of any abnormal stimulus and probably existed normally in the living animal, though less evident in the amphibia than in the tortoise. That they were myogenic in origin seemed to follow from the inhibitory effect of potassium hydroxide solutions and chloroform, both of which are muscle tissue poisons. Impressed with the slow rhythmic nature of the contractions which reminded him of pseudopoidal movements in the amoeba, and their occurrence only in cells rich in cytoplasm, Bottazzi (10) presented his well-known sarcoplasmic theory of tonic muscular contraction. According to this the tonus oscillations are simply independent contractions and expansions of the sarcoplasm which supports the anisotropic substance in its quicker contraction.

Gaskell (35) criticized the sarcoplasmic theory at once since he had never observed tonus oscillations in the land tortoise and they are absent except very rarely in the ventricle. Although Cobb (19) justly remarks that there has never been any real proof anatomically or physiologically that sarcoplasm is contractile, and although the original observations are now believed to apply to smooth muscle only, as will be detailed in a moment, yet the idea either in its original form or the later one of physico-chemical changes in the cytoplasm which delay relaxation, has been widely accepted, as may be seen from such recent writers as Hunt (51) and Riesser (72).

Bottazzi fully realized that to interpret a phenomenon as tonus one must be on his guard that there has not been merely a change in the course of the fundamental contractions. He therefore studied with great care the influence of various factors, particularly nervous ones, on the tone waves (11,15) to make absolutely sure he was dealing with primary and not secondary effects. By carefully grading his stimuli he found that he could by vagal stimulation secure an increase in tonus, a positive tonotropic effect, before any negative chronotropic or inotropic effects on the normal contractions appeared. On stimulating the accelerators he secured a decrease in tonus, negative tonotropic effect, before the positive chronotropic and inotropic effects on the regular contractions appeared. Thus the nervous control of the auricular tonus oscillations was elucidated and a further proof offered that the phenomenon

depended on some other structure than that concerned with the fundamental systolic contractions.

The similarity between auricular tone changes and the contractions of smooth muscle was studied by Bottazzi and Grünbaum (12). They found the two tissues are much alike in their responses to temperature and various drugs, and this they regarded as confirmation of the sarcoplasmic theory since both muscles were rich in that material.

The next chapter in the story of auricular tonus was Rosenzweig's (74) discovery of a sheath of smooth muscle cells underneath the endocardium of Emys europaea. This work was confirmed by Bottazzi (14, 16) and Bottazzi and Ganfini (13) and from this time the auricular tonus waves of the cold-blooded forms have been generally referred to this tissue. Laurens (57) also investigated this subject, finding smooth muscle much as Rosenzweig and Bottazzi had described it. In addition Laurens made the interesting observation that Lacerta viridis, a lizard in which neither he nor Bottazzi could ever see tone waves, was devoid of smooth muscle in its auricles. Recently Shaner (78) has made a hisological study of the occurrence of smooth muscle in the turtle's heart. He finds that the tissue can be traced from the sinus through the atria into the ventricle and even out into the conus and great arteries. The layer is thin and interrupted in the sinus but in the atria the coat is far heavier. In the ventricle it breaks up into strands and penetrates the deepest recesses. The evidence then seems to indicate that there is quite enough smooth muscle present to account for tone waves in the auricle of certain cold-blooded forms, but too little of the tissue to allow them to occur in the ventricle. It would also seem a fair conclusion that the striated cardiac musculature could not produce tonus waves. It is to be noted that the sarcoplasmic theory has had removed from its realm the very tissue on which it was supposed to be founded.

Interest in the tonus waves did not cease however with these anatomical discoveries. Oinuma (65) in 1910 again covered the field confirming Fano and Bottazzi on all major points particularly in regard to nervous control which had been questioned by Rosenzweig. In recent papers Gruber (39, 40, 41, 42, 43) has studied the action of a number of drugs on tonus waves in the terrapin. The results for the most part were what one would expect if the action were on smooth muscle. Adrenalin caused the waves to disappear while KCl, nicotine, digitalis and $BaCl_2$ increased them. Adrenalin and KCl were shown to be antagonistic. In his studies on the tortoise auricle Porter (70) found that the tonus contractions could be superposed and built into

tonus tetanus. This led him to the hypothesis that tetanus was essentially the same in smooth, cardiac and skeletal muscle, a fusion of tonic contractions. Pereira (68) found, contrary to Fano, that warming the perfusate augmented the tonus waves. Gesell (38) has made an interesting use of the tonus oscillations in the tortoise auricle to study the effect of length of fiber and initial tension on cardiac function. By taking advantage of the tonus waves and allowing the auricles to contract isotonically or isometrically it was possible to vary the length of fiber with initial tension constant or to vary initial tension with length of fiber constant.

More recently Snyder and Andrus (79) have sought to identify the tissue responsible for tonus in the terrapin heart by means of chemical stimulation. They were able to elicit tone changes by perfusates having appropriate H-ion concentrations. If these were due to contraction of the smooth muscle, they argued that smooth muscle poisons such as papaverin and benzaldehyde should not only depress tonus waves in the auricle but should also abolish the stimulating effect of the appropriate pH solution. This was found to be the case.

The evidence that tonus waves in the cold-blooded heart are due not to the striated cardiac muscle but to the smooth muscle sheath is thus fairly conclusive. Whatever the tissue that may be responsible for them, they remain, however, auricular tonus waves and they must bear some relation to the circulation. Only a few suggestions have been made as to their possible physiological functions. Fano thought that by decreasing the width of the auricle they might have something to do with directing the greater and lesser circulations in the ventricle, although the exact mechanism was never very clearly expressed. Bottazzi believed that the tonus waves in some way supported the auricular contractions and allowed more complete contractions much as afterweighting does for skeletal muscle. It may be objected that it is difficult to see just how the cardiac muscle could be equally well supported in both phases of a tonus wave. Since tonus waves occur most often in those conditions which have a weakening effect on the systolic contractions, such as vagal effects, cold, and hemorrhage, Oinuma suggested that they might be related to ventricular discharge. Tonically contracted auricles would have a reduced volume and the ventricle would therefore receive less blood at each auricular systole. In certain conditions this might be of advantage to the organism. For example, during the period of winter sleep the increase of the tonus waves due to the cold might spare the ventricle and adapt its output to the lowered needs of the body.

Tonus waves in the ventricle. Tonus waves in the ventricle of the cold blooded heart are rarely seen. Fano (23) saw them only three times in over 100 experiments and any one who has repeatedly produced heart block with an Engelmann clamp knows their rarity. Howell on the contrary in his textbook states that strips from the terrapin's ventricle do often vary in length with differences in conditions and not infrequently these changes take on a rhythmical character.

In the mammalian heart spontaneous changes in diastolic length of fiber are seldom seen if the temperature and composition of the perfusate are well controlled. A few workers have however reported tonus waves in these forms. Although Busquet and Tiffeneau (18) and Stefani (84) have seen such oscillations in the isolated rabbit's heart, the phenomenon was usually fleeting and only occasional in occurrence. The authors suggested an explanation based on variations in conductivity. After drugs a few investigators have also described rhythmical oscillations of tonus. Kuliabko (59) reported such tracings after perfusing rabbits' hearts with small amounts of veratrine.

The effect of the cardiac nerves on ventricular tonus. The fact that the ventricles do not ordinarily show spontaneous tone variations similar to the tortoise auricle of course does not exclude a certain degree of sustained contraction throughout diastole. As a matter of fact as soon as the marked dilatation resulting from strong vagal stimulation was noted, physiologists interpreted it as a decrease in normal cardiac tonus. Among those who have held this view are such illustrious names as Coats, Heidenhain, Gaskell, Stefani and Francois-Franck. Even today the same idea often reappears, and almost every type of dilatation is felt to indicate a loss in tonus. It is mainly to the work of Otto Frank, and Hofmann, that we must turn for a finished treatment of this subject. Although their papers are now many years old the essential points are worthy of detail.

Frank (28, 29) derived his laws of cardiodynamics from experiments on the frog's heart in which he could at will record either isometric or isotonic contractions. By varying the degree of cardiac filling and plotting the systolic and diastolic pressures against the volume, Frank obtained two sets of two curves each, one the extension curves of the isotonic maxima and minima and the other the extension curves of the isometric maxima and minima. The extension curve of the isometric minima through part of its course runs at a lower level than the isotonic minima, which is due to the fact that in an isometric contraction the relaxation of the heart takes place more rapidly than it does in an

isotonic. This observation on the different degrees of relaxation in the two types of contraction at once emphasizes the difficulty in proposing a consistent definition for the word tonus. The effect of vagus stimulation on the diastolic curves is the point of greatest interest here. The extension curve of the isometric minima was in general unchanged, and since relaxation in the isometric contractions is rapid and complete this extension curve may be regarded as that of the resting heart. For isotonic contractions the extension minima was lowered by vagus stimulation only for those pressures at which the diastolic portion of the contraction curves had not yet approached the horizontal, that is, the heart was still relaxing. Even in these cases the extension minima was never lowered below the isometric minima. Frank's work on this particular subject may be summarized in a word by saying that vagal stimulation does not result in any change in the extension curve of the resting heart.

From his experiments on the isolated frog's heart with suspension methods Hofmann (48) came to conclusions much the same as those just detailed. In testing for a possible vagal effect on tonus he noted that two indirect effects must be guarded against. The first of these was observed by Gaskell. Since the ventricle relaxes slowly the bottom of the curves will vary in position with the heart rate. If the rate is fast there will not be sufficient time for relaxation and the base line will be high. If the rate is slow relaxation will be more complete and the base line will be lowered. The vagus must then not be credited with a result due entirely to changes in rate. The second indirect effect depends on changes induced in the course of the contraction curves themselves by vagal stimulation. In the amphibian heart an inotropic effect even without a change in rate is accompanied by a shorter systole, an earlier diastole, and hence a shortening of the whole course of contraction. The result of this is that although the rate may remain or be held constant by artificial stimuli, yet the interval between successive systoles during vagal stimulation is lengthened and more time thereby given for relaxation. In this way the vagus may seem to lower tonus without, however, having anything to do with the reduction of a constant sustained contraction such as we assume tonus to be. Hofmann justified his conclusions by many direct experiments. In the resting auricle although a positive variation appears during vagal stimulation, as Gaskell has shown, he was never able to see the slightest change in form. If a heart were made to beat every 3 seconds by artificial stimuli, vagal stimulation brought on a considerable lowering of the diastolic base

line; with stimuli every 10 seconds the vagal effect was noticeably less; when the stimuli were given every 15 seconds the vagal effect disappeared. He also secured many curves showing only a negative inotropic effect but with this there was the shortening of the contraction cycles, the longer interval between, and the resulting relaxation.

As already mentioned Gaskell was well aware of the effect of rate on the degree of diastolic relaxation, but he overlooked the earlier appearance of diastole and the shortening of the cycle which comes with vagal stimulation. For this reason he felt that a lowering of the diastolic base line without a change in rate was sufficient evidence of tonus. If his figure 25a on plate 70 (36) be examined the greater speed of relaxation and the longer intervals may be noted, although rate was unchanged. Loss of tonus was here again a secondary effect and not a primary one.

Recently Bohnenkamp (8) has analyzed the effects of vagal and accelerator stimulation of the contraction curves of the frog's ventricle. He confirms the older workers by finding an earlier and more abrupt diastole and a shortened systole. There may be a hastening of relaxation even before any inotropic effect is noted. This observation is important for it shows that an increased period for relaxation may appear between beats even before rate or height of contraction are affected. In such cases the consequent descent of the diastolic level in the curves could of course not be used as an argument for tonus.

There is practically no literature on the effect of the vagus on the tonus of the mammalian ventricle. Although stimulation of the vagus is known to diminish the strength of auricular contraction in the mammalian auricle (20) any conclusive evidence of its effect on the ventricle is lacking. It is true that certain changes appear in the ventricular volume curves, for example, a lengthening of the systolic phase (89), but such variations are usually assigned to the variations in diastolic filling and the resulting initial volumes and tensions, rather than to direct vagal influences. Whether or not the vagus exerts any effect on the ventricle is an old physiological controversy but since the work of Cullis and Tribe (20) the idea has been rather generally abandoned. It will be remembered that these workers found that after section of the A-V bundle, pilocarpine and muscarine no longer had any influence on the ventricle, although the auricular effects were still evident. Recently Fredericq (30, 31) has shown a reduction in the chronaxie of the cold blooded and mammalian ventricle following vagal stimulation. This increase in the spread of excitation he believes to be due to a direct

action of the vagus on the myocardium. Fredericq has made no mention of any tonic effects.

Stimulation of the accelerators has also given little evidence of tonus either in the cold-blooded or mammalian heart. Frank (29) could not find that excitation of these nerves caused any change in the extension curves of either the isotonic or isometric minima. He therefore dismissed the subject with only a word. Since the duration of contraction is lengthened in the frog's ventricle by stimulation of the sympathetics (Bohnenkamp) a decrease in the extent of relaxation might be expected with the usual interpretation of a change in tonus. The literature does not seem, however, to record such experiments. In the mammalian heart it was shown by the early workers that the accelerators shortened systole but it was not clear whether or not the action was directly on the ventricle. The experiments which showed changes in intraventricular pressure are now known to be due to secondary causes. Henderson and Barringer (45) maintained that no augmentor effects could be obtained unless the arterial pressure was low and the musculature in a condition of diminished vigor. Even then they felt the influence of the nerves was of little consequence. Wiggers and Katz (90) and Katz (53) have investigated this point and by using systole-cycle ratios to eliminate the effect of rate itself have come to the conclusion that the accelerators do have a specific effect on the ventricular musculature which reduces the contraction period. Important as these results may be they throw very little light on the tonus problem.

There are a few experiments among the older workers that have been felt to have possible significance even in the face of the negative results related. Gaskell (36) presents a volume curve from a frog's ventricle in Roy's tonometer in which on vagal stimulation there is a drop in the diastolic level without a change in rate. It was this experiment that led him to assign the property of tonicity to the amphibian ventricle. The speed of the drum is not fast enough to analyze each contraction. In the light of our present knowledge it is probable that the diastolic extension was due to the earlier appearance of diastole in each cycle which would give extra time for a more complete relaxation. Francois-Franck (27) found by applying a lever to the heart wall that on vagal stimulation there was evidence of softening of the muscle. It is quite doubtful if such a method is adequate to indicate a change in tonus.

From the above discussion it may be concluded that no satisfactory evidence exists that the cardiac nerves control any property of the ventricular muscle that is comparable to tonus within the sense of our

definition. The variations in relaxation which occur may all be explained by changes in the course of the contraction itself and careful analysis of all the experiments so far reported not only removes the need, but actually excludes the possibility of a sustained contraction controlled by nervous influences.

Attempts to locate supraventricular tone centers. With the failure of all attempts to show that there is any kind of a permanent diastolic contraction under extrinsic cardiac nerve control, a number of authors have recently devoted themselves to the proposition that there is a ventricular tonus under the control of supraventricular tonus centers. The work has necessarily been carried out on cold-blooded hearts.

In 1917 Pietrkowski (69) inflated the auricles of a frog by injecting air into them with a syringe until they were well distended. He then noted that under these conditions the ventricle went into a state of tonic contraction much as the frog's heart does when digitalized. Stretching the auricles actually sensitized the ventricles for succeeding doses of digitalis, $BaCl_2$, $CaCl_2$ and methyl violet, and in this he thought he saw something similar to the sensitivity which clinical cases exhibit to digitalis. Pietrkowski interpreted his results to mean that the auricle possessed some kind of a tonus center which was connected to the ventricle by muscular pathways. In this way the tonus condition of the ventricle could be modified.

Two years later Loewe (58) made similar observations, finding that ventricular tonus could be increased on distending the auricles with normal salt solution quite as well as with air. On studying ventricular strips he noted that while they lived many hours even without oxygen and responded normally to many drugs they were abnormal in two respects; their tonus relations and their reactions to members of the digitalis group. There was never any indication of tonus changes in the strips and digitalis was entirely without effect. On the other hand a strip of digitalized auricle either beating spontaneously or in a standstill from the drug, responded to stretching by a long sustained maximal tonic contraction. An isolated ventricular strip similarly treated would not do this unless it were connected to the auricle. The response then appeared on stretching either auricle or ventricle. After cocain this stretch reaction could not be secured. From all of these observations Loewe concluded that he was dealing with an intracardial nervous reflex tonus mechanism. The center was located in the auricle where ganglia were known to exist and to this came afferent connections from both auricles and ventricle and from it went efferent pathways to both

auricular and ventricular muscle. At first the stretch reflex could only be demonstrated after some kind of sensitization with digitalis, but later it was secured in the normal heart by distention with saline.

Wichels (86) came to the same conclusions as Loewe. He found that only strips in connection with a ganglionated portion would give the stretch reflex after digitalis treatment and that cocain abolished the response but it did not interfere with automaticity. He too therefore decided in favor of an intracardial nervous reflex mechanism which governed tonus.

From a study of the contracture-producing drugs, Fröhlich and Pick (32) believed that there were nervous contracture and tonus centers located above the ventricle, probably in the auricular septum. Their argument was that they found chloral had but little action in raising the diastolic level of the ventricular contraction curves unless the ventricle were left connected to the sinus and auricle. They also noted that occasionally the $BaCl_2$ contracture of the ventricle could be seen to increase and decrease spontaneously which seemed to indicate some kind of nerve action.

In their study of strophanthin Amsler and Pick (2) in 1920 gave evidence of a contracture inhibitory center somewhere above the ventricle. These authors found that if the ventricle of the frog's heart were divided into a right and a left half, one isolated and the other left in connection with the auricles, the latter did not go into contracture on being bathed with a strophanthin solution, but the half completely isolated from the rest of the heart promptly passed into a state of exaggerated tonus. Their proposed center, inhibitory to the development of contracture, was not the specialized motor center of the heart for if the sinus were depressed chronotropically the ventricular contracture still did not appear in the ventricle.

Simultaneously with the above studies the work of Szent-Györgyi (85) appeared which seemed to indicate that under normal conditions there was a ventricular tonus under sinus control. After tying off the sinus of the frog's heart the ventricular beats, judged by suspension curves, at once showed three important variations. The curves lengthened due to a greater diastolic filling, the diastolic descent was steeper showing a quicker relaxation, and there was a short series of after vibrations similar to those described by Emanuel for atonic muscle. All these changes Szent-Györgyi interpreted as being due to a loss of tonic influences from the sinus.

In 1922 Regelsberger (71) confirmed and amplified the work of Szent-

Györgyi. He modified the previous technique in several ways. Injury to the A-V groove was avoided, the sinus was eliminated by the milder methods of cooling or application of urethane, and to meet the criticism of a change in rate the ventricle was kept at a uniform rate by artificial stimulation. In one group of hearts he succeeded in demonstrating a loss of ventricular tonus, i.e., a lower diastolic level of the suspension curves, on extirpation of the sinus by any of the methods mentioned. He had however to admit that there was a second group of toneless hearts that gave no response to any of his procedures.

The papers mentioned thus far would seem to make an excellent case for ventricular tonus under supraventricular control in the cold-blooded heart. On close examination, however, it is noticeable that with the exception of Regelsberger no attention whatever has been paid to the fundamental principles for judging the presence of tonus laid down particularly by Frank and Hoffman, and often the technique is by no means above reproach. This has led to a repetition of many of the experiments and a great deal of merciless criticism from recent workers such as Machiela (60), Koch (54), Holzlöhner (49) and Rössler (75).

In Pietrkowski's experiments it is unbelievable that some air was not forced into the ventricle on blowing up the auricles, due to incompetence of the valves, and that the ventricle was not thereby somewhat distended. That stretching of the ventricle may bring on a certain degree of maintained shortening or even a systolic standstill has been known since the work of Goltz in 1862 (see Koch for literature), and has been confirmed by many workers since. If the auricles are blown up without any of the pressure being allowed to reach the ventricle, a feat that Koch accomplished by closing off the A-V orifices with a tiny rubber balloon, then there is no appearance whatever of the so-called ventricular tonus. Whatever the real nature of this ventricular stretch reaction may be, it has to do with the course of the contraction itself and does not depend on any supraventricular influence. Pietrkowski's work offers no real evidence for the existence of a tonus center in the auricles.

The experiments of Loewe and Wichels were repeated by Machiela with exactly opposite results. Typical strophanthin contracture was secured from strips taken from any part of the heart, no matter whether they were attached to the auricle or entirely isolated. Machiela attributed Loewe's failures to get his stretched reflex on isolated strips to an insufficient oxygen supply and to overloading. Strophanthus does not bring on contracture unless the oxygen is adequate, and the loads borne

by the muscle strips do not exceed 0.32 to 0.75 gram. If these precautions were observed Machiela secured contracture with the greatest ease. These newer experiments entirely remove the necessity of postulating supraventricular tone centers to explain the action of the digitalis like bodies.

The work of Fröhlich and Pick has been reviewed by Amsler and Fröblich (3). The latter authors find no need of bringing in any higher centers to explain the action of chloral. The drug in some way predisposes ventricular muscle to contracture. Whenever the rate of contraction is sufficiently rapid the contracture appears. If the strip or entire ventricle is left attached to the sinus and auricle, the normal rate is fast enough to bring the ventricle into contracture. The automatic ventricle does not usually beat rapidly enough. In this case artificial stimuli may be applied at a faster tempo and contracture at once appears.

No one has apparently repeated the experiments of Amsler and Pick (2) on strophanthin contracture. It is evident that they are out of agreement both with Loewe and Machiela. It is probable that as in Loewe's work a removal of all technical difficulties would leave no necessity for invoking inhibitory tonus centers. Rössler has compared, however, the contraction curves obtained from an isolated half ventricle with that secured from the other half of the ventricle which was still connected to the upper parts of the heart. The isolated half gave a larger curve than the half still attached, but the extra height was due to an increase in systole and not to a more marked relaxation. The important point here is that the entire course of contraction is modified in the automatic beat of an isolated portion of a ventricle, and a change in the contour of such a curve can hardly be used as evidence for the sudden appearance of tonus and much less for the idea that tonus had been previously inhibited by a higher center.

The strongest support for supraventricular tone centers was apparently contained in the work of Szent-Györgyi and Regelsberger, and yet almost every detail of their experiments has been subjected to criticism by Koch and Holzlöhner. Szent-Györgi based his conclusions on the appearance of greater relaxation, a steeper descent of diastole, and certain elastic after-effects, all of which could be seen in the ventricular curves following elimination of the sinus, but that these were due to a loss of tonic influences from the sinus by no means necessarily follows. Any or all of these effects might be due to changes in rate or to inaccuracies of the recording system. Both of these seem as a matter of

fact to have been present. Koch actually duplicated the curves in his own experiments by artificially varying the rate of contraction and adjusting the mass of the recording levers. Szent-Györgyi's curves taken before tying off the sinus do not show a horizontal diastolic level between systoles, but after removal of the sinus this begins to appear. The explanation of the supposed loss of tonus is simply that the automatic ventricular rate following sinus removal is slow enough to allow time for a greater relaxation. The steeper diastolic descent and the after oscillations are due to the influence of the lever mass, which because of the slow rate is now able to express itself. It is true Szent-Györgyi attempted to control the effects of a change in rate by depressing the sinus rhythm with perfusion solutions deficient in CO_2 to a point at which the ventricle became automatic. As the sinus ceased to function a decrease in tonus appeared. No curves were however presented to illustrate this, and in a previous publication (61) dealing with the action of CO_2 no mention is made of such results.

Regelsberger's success in demonstrating a loss of tonus after sinus extirpation seems also to have depended on technical errors. Koch found in 41 experiments that if the load were light, then on eliminating the sinus the ventricular rate following was slow enough to allow time for a more complete relaxation. If however the load were heavy enough fully to distend the ventricle at its sinus rate no further extension occurred when the sinus was extirpated even though the rhythm was slower. Regelsberger's two classes of tonic and toneless hearts were then probably determined by differences in loading. It is also likely as pointed out by Rössler that the lowering of the diastolic level in some of Regelsberger's curves was due not to any so-called tonus decrease but to the failure of the auricle any longer to compensate for the ventricular movement since its time of contraction had varied in the new rhythm. To avoid any error due to the slower rate after removal of the sinus Regelsberger threw the heart into an artificial rhythm by electrical stimulation. With this fixed rate he still found the diastolic level of his curves lowered on sinus removal. The contour of the curves was changed which robbed them of much of their value as evidence. Moreover Koch in 10 experiments was unable to determine any change whatever in diastolic relaxation if the heart was kept in a constant artificial rhythm during the sinus removal.

It may not be quite fair to throw entirely out of court all of the attempts to prove supraventricular tone centers but certainly a verdict of not yet proved must be brought in. The workers so far have not

fully recognized that neither an increase nor a decrease in diastolic length can be accepted as a proof of tonus so long as it is accompanied by variations in rhythm or a modification in the course of contraction. The evidence thus far has not met these qualifications.

Variations in the composition of perfusion fluids. On first thought variations in the chemical composition of the fluid supplying the heart, either normally or in artificial perfusions, might be expected to offer a means of attacking the tonus problem. Such experiments, though important enough for certain purposes, have been very disappointing for the question in hand. The reasons for this are quite obvious. In the first place most, if not all, the substances modifying the degree of diastolic relaxation, distort the course of the normal contraction which shows that the processes underlying the contraction are disturbed, and any conclusion regarding tonus is at once rendered difficult or impossible. In the second place, even if a chemical substance should bring on a shift in the diastolic level without changing the course of the individual contractions the interpretation would be none the less difficult. The result might be due to an increase or decrease in a contraction sustained throughout diastole, i.e., tonus, or it might be a physico-chemical change in the diastolic phase which allowed a different type of relaxation, or a physico-chemical change which modified the elastic properties of the musculature.

The variation in the perfusion fluids which has been of most interest in this connection is that of its reaction. Gaskell (34) long ago noted that an alkaline solution perfused through the heart brought on a systolic standstill while perfusion with an acid solution induced a standstill in diastole. These results were attributed by Gaskell to changes in tonicity of the heart muscle although he frankly admitted he did not know the mechanism involved, whether it was an idiomuscular contraction or a change in elasticity. In recent years the exact pH values that give these results have been determined, Andrus (4) showing that a pH of 7.4 to 7.6 augments the tonus of the turtle heart while a pH of 7.4 to 7.3 decreases it. Some of the theories proposed in explanation of these actions may be found in papers by Andrus (5) and Mines (63).

Similar observations have recently been made on the mammalian heart. Iwai (52) found in the isolated cat's heart that a change of pH from 7.4 to 7.5 brought on increased diastolic tone while a change to pH 7.2 caused a diastolic relaxation. It is impossible to tell from the evidence presented the exact nature of the relaxation. Whatever its course, a heart supplied with blood of a low pH apparently shows a

greater relaxation in diastole. For a given venous pressure this would allow not only a more complete filling of the ventricles but, what is of more importance a faster distention. Barr and Himwich (6) have shown that in exercise the pH of the blood may change from 7.3 to 7.1. This is apparently sufficient to affect the heart and it may be that here we have a chemical control of the resistance the heart offers to diastolic distention. If in exercise the heart could fill more rapidly, then even at higher rates it might still put out more nearly the normal amount of blood per beat, which would help very materially in explaining the large minute volumes found in severe exercise. It is evident that volume curves would not always be superimposable if such a mechanism should be found to exist.

Another well-known example of increase or decrease in diastolic relaxation depends upon the calcium and potassium content of the fluids that bathe the heart, potassium promoting and calcium inhibiting relaxation. These changes are entirely independent of rate, neither do they depend upon the variation of any kind of sustained diastolic contraction. Their action depends on modification of the contraction and relaxation processes themselves as may be seen by curves taken rapidly enough to allow a study of the different phases. Potassium brings about a slower systole and a more rapid diastole, while calcium hastens systole but delays diastole. Holzlöhner (49, 50) has recently discussed the actions of the Na, Ca and K ions and his papers will supply references to this literature. I_t is evident that to speak of tonus being increased by calcium or lowered by potassium is to use the word in a very limited sense. We do not know the exact nature of the processes concerned, but they are certainly special physico-chemical reactions of some kind having to do with the protoplasm of the muscle cell and modifying the normal course of contraction in particular ways. Suggestions of possible mechanisms involved may be found in the work of Otto Frank as well as in the recent investigations of Gasser and Hill (37) on the viscous-elastic properties of muscle. Neither calcium nor potassium is known to vary sufficiently in concentration in the blood during any activity of the body so that a physiological function could be assigned to the relaxing or contracting properties of these substances. For all these reasons it is not believed that calcium or potassium offer any evidence in favor of a continuous state of contraction in heart muscle.

Contractures. Cardiac muscle in common with skeletal on exposure to many chemical substances enters into a state of long sustained contraction commonly known as "contracture." This may be brought

about by extremes of H-ion concentration, excessive calcium content, or the action of a number of drugs such as chloroform, caffein, alcohol, digitalis and many others. Many writers have insisted on referring to these contractions as examples of tonus. Such a use of the word is however quite unjustified if we conform to the definition adopted by the reviewer, for the contractures are very clearly due to marked disturbances in the normal rhythmical contractile processes and have nothing directly to do with sustained diastolic contraction. They are exaggerated contraction remainders. Meyerhof (62) claims that all contracture forming substances cause a lactic acid formation in the muscle which accounts for the contraction. Following this there is a failure to relax due probably to some physico-chemical action of the substances themselves on the proteins of the muscle. Bethe and his pupils (7) do not believe that the contracture producing substances act in a round about fashion by forming lactic acid, but that they stimulate the contractile substances directly. Both views are accepted by Riesser and Heianzan (73) since they have shown that in acetylcholin contracture no lactic acid is formed. These views of recent workers are mentioned to show that no one familiar with the field has attributed contracture to an increase in a previous state of sustained contraction.

Action currents. If there is a condition of sustained contraction in the heart one would expect that the galvanometer string when connected for monophasic curves, would show a displacement from the position of rest. No such records have, however, been reported. On the contrary Evans (22) found that in the snail's heart with the induction of a state of tonic contraction by excess carbon dioxide, the electrical changes ceased and there was a return to the iso-electric state. Schäffer (77) has shown a long slow return of the string to the iso-electric point after a contraction in the quiescent frog's ventricle. From this he argues that the heart during a series of beats is in a constant state of tonic excitation. Since the negative condition slowly passes off after a single beat or a series of beats, it is evident that the phenomenon is associated not with any continued state of contraction but most likely with the chemical changes associated with relaxation.

Too much cannot be expected from this method in the study of cardiac tonus when there is yet no agreement that electrical phenomena are associated with tonus or even contracture of skeletal muscle. Adrian (1) and Cobb (19) are both very skeptical of the positive results so far reported, believing that the technical difficulties have not been overcome by the investigators. Very recently however Schäffer and Licht

(76) have found a long monophasic variation associated with acetylcholin contracture.

Special contributions that have touched on tonus. There have been many contributions to specific problems of circulation that have contained interesting references and observations on cardiac tonus. It is difficult to place them in any definite category but a few of the important ones will be mentioned briefly here.

In a study of weakness induced in the frog's heart by overexertion from a long rapid series of contractions Bruns (17) has noted variations in diastolic and systolic volumes independent of rate and distending pressure. These spontaneous changes were more marked in the exhausted hearts and there seems no doubt that they were tonus oscillations similar to those occasionally found by other workers in the cold-blooded ventricle. On gradually increasing the pressure of distention the fatigued hearts were found to be more extensible than fresh ones. This extensibility was attributed to a change in elasticity; at least the hearts showed elastic after-effects and other characteristics of elastic bodies, which are obscured in fresh hearts with good contractile power. Since Rohde showed that the dynamic laws of the cold-blooded heart apply to the warm-blooded, Bruns concluded that increased extension due to fatigue might play a part in cardiac dilatation.

Socin (80) studied the acute cardiac weakness produced in the heart-lung preparation of the cat on inhalation of chloroform. A dilatation resulted in all cases but the plethysmograph showed that it was due to a weakening of the musculature which left more blood behind after each systole. In five experiments there was some evidence that dilatation appeared before a decrease in the stroke volume. If this were substantiated it would speak for a change in diastolic extensibility which might be referred to changes in elasticity or in a sustained diastolic contraction. Socin did not feel however that his technique was accurate enough to justify such a conclusion. The work is well worth repeating from this point of view.

The work diagrams constructed by Straub (82) have given some interesting information about diastolic conditions in the mammalian heart. Even toward the end of diastole the diagram is convex to the abscissa which means that a certain degree of contraction remainder has persisted throughout nearly all of the filling time. From this it can be safely concluded just as Frank found in the frog's heart, that under all ordinary conditions the curve of the extension minima of the mammalian heart does not lie on the curve of the extension minima of the

resting heart but above it. An increased diastolic relaxation is then in itself no more evidence of tonus in the mammalian heart than it is in the cold-blooded. By comparing work diagrams from hearts subjected to injury with those from fresh hearts Straub showed that muscular weakness did not express itself in any change in the position of the extension minima. In other words, fatigue was without any effect on the degree of diastolic relaxation. This agrees with the work of Socin but differs from the results obtained by Bruns. The latter, however, subjected his preparations to extremes not likely to be met even in pathological cases. In the fatigued hearts Straub found constantly a lowering of the extension maxima. Injury to the heart is thus seen to result in weakening of the contractile power and decreased expulsion of blood. The diastolic dilatation that ensues is then in no sense due to a change in tonus.

In his many experiments on the volume changes of the mammalian heart, Henderson (46) has abundant references to cardiac tonus. He agrees with Frank and Hofmann that vagus stimulation has no primary effect on the diastolic curve. Henderson's definition of tonus as "the height of the coefficiency of elasticity, and hence the degree of resistance to deformation," gives very little light on his conception of its real nature. It is obvious however that the diastolic resistance to distention must run a uniform course if all volume curves are to be superimposable and the law of uniform cardiac behavior valid, so he infers an entire absence of those stimuli which induce tone in a resting skeletal muscle. The only factor that normally influences tonus in Henderson's sense, is the rate; tonus being high at rapid rates and wearing off in vagus standstill. Henderson's tonus is then the "contraction remainder," the amount of which is an individual peculiarity varying but little for each heart. Tonus may then vary with the rate for the faster the beats occur the more there is of the contraction remainder present and the smaller is the diastolic size. The resistance offered to distention by this form of tonus is greater than all normal venous pressures, else the relaxation curve would vary with the venous pressure. It is evident that Henderson's whole theory of the mechanics of the heart beat depends on this conception of tonus. Although he is often cited as a firm believer in cardiac tonus, in no place that we can find does Henderson ever argue for any form of sustained diastolic contraction independent of the regular contractions. To admit such a phenomenon would be inconsistent with his whole point of view. The condition of extreme tonus to which he refers in acapnia is a contracture either of a greatly fatigued or poisoned muscle.

Reference has already been made to Starling's views on tonus. He does not believe that during the diastole of a normal heart there is a trace of a state of tonic contraction (81). The dimension which the heart attains during diastole is a function of the length of the diastolic period and of the speed with which the blood enters the heart. In the contracted heart of shock there is no augmentation of tonus but merely a decreased venous return due to stasis in the capillaries. Likewise a cardiac dilatation may have nothing to do with decreased tonus but depend merely upon the amount of blood entering the heart, according to the principles expressed in the law of the heart. The increased diastolic size following increased peripheral resistance or weakening of the myocardial musculature is according to this interpretation brought about by a temporary decrease in output per beat accompanied by the regular inflow. The heart thus dilates not because a sustained diastolic contraction is reduced but because of the increased amount of blood in the heart, and this form of dilatation continues until the heart fibers have increased in length sufficiently again to meet the circulatory demands.

The disbelief of Starling and his collaborators (66, 67) in tonus rests on their experiments which showed very little or no change in intraventricular diastolic pressures. They found the fall of pressure at the end of systole occurred just as rapidly as the systolic rise. The curve fell to the zero line and then in most cases rose gradually but very slightly during diastole. At times the pressure remained at approximately zero during the greater part of diastole. For these reasons they felt that the pressure necessary to distend the heart was negligible for a rather wide range of inflow. Since the low diastolic pressures indicated that there was little resistance to distention there could be of course no sustained diastolic contraction.

If diastolic tone were present intraventricular pressure would hardly fall to the zero level after the opening of the A-V valves, and there would certainly be a definite positive pressure throughout diastole, with an increase toward the end of the period. Although an examination of intraventricular pressure curves by various authors often shows a higher pressure during diastole than one might expect from Starling's description, Wiggers (91) for example, finding a definite increase at the end of diastole in 28 per cent of his intra-auricular records, there is not sufficient evidence from this source to warrant a belief in tonus. Furthermore, if there were any kind of a sustained diastolic contraction that could be termed physiological one would expect to find numerous fluctuations

both in pressure and volume curves. As is well known, for any given experiment under anything like normal conditions these are remarkably constant and uniform. In view of all this, it is not surprising that Starling has abandoned any idea of diastolic tone. His appropriation of the term for the contractile fitness of the fiber has however not helped in clarifying the question and in the reviewer's opinion such use of the word should be discontinued.

Tonus and dilatation. This is not the place to discuss the vast clinical and experimental literature that has accumulated on cardiac dilatation. The widespread belief, based however on a very meager experimental basis, that dilatation is associated with hypertrophy, justifies a reference to the possible part played by tonus. Following the classification of Moritz (64) dilatations may be said to be *tonogenic* or *myogenic.* A tonogenic dilatation is one that results from any increase of tension in the muscle and it is characterized by an increase in both initial and maximal intraventricular pressures and a maintenance or increase in stroke volume. Such a dilatation is entirely passive being due to an increased filling pressure because of a more rapid venous return, a lengthening of the cycle, or the inability for a few beats to empty against a heightened peripheral resistance. The heart quickly compensates and the entire process may be said to be physiological. The term myogenic Moritz used for a dilatation due to muscle weakness or injury. In this case although the heart is dilated it does not increase its output. Straub (83) has pointed out that the two types can only be distinguished when the peripheral resistance which is to be overcome is known.

Hering (47) has subdivided the myogenic dilatations into two classes, the hypinogenous or those that arise from a decrease in the contractile power of the muscle, and the hypotonogenous or those caused by a decrease in muscular tonus. The lengthening of the fibers in the latter case according to Hering is due to a vital physiological process. Hering's theory of hypotonogenous dilatation rests on the experiments purporting to show a supraventricular control of ventricular tonus which we have already reviewed. Although clinicians have been favorable to such views (56, 59) until the evidence becomes much more convincing one can scarcely accept an atonic type of dilatation.

SUMMARY

In cardiac physiology the word tonus has been used both by physiologists and clinicians in so many different ways that an attempt has been made to define the term. Cardiac tonus is a condition of sus-

tained diastolic contraction, independent of the systolic contractions, by virtue of which the muscle fibers resist distention more than they would because of their mere physical properties. In testing for cardiac tonus in this sense it is necessary to find spontaneous changes in diastolic relaxation or changes due to variations within normal limits of some physiological condition. Relaxation due to slower rates, modification in the course of the systolic contraction, or pressures outside the normal must be excluded since they are not primary but secondary in their action. It must be kept always in mind that the diastolic size of the heart in itself offers no evidence of tonus unless all other factors are controlled. By definition contraction remainders, contractures, elasticity and variations in the contractile power are not regarded as tonus. The action of drugs cannot be expected to furnish evidence for the existence of cardiac tonus.

There is general agreement that tonus waves occur in the tortoise auricle, although recent workers attribute them to the rythmical contraction of a smooth muscle sheath. In the ventricles of all forms tonus waves have been reported only occasionally. The view, still widely current, that the vagus may induce greater ventricular diastolic relaxation is not consistent with the classical work of Frank or Hoffmann and is unsupported by any convincing recent experimentation. The existence of supraventricular tone centers has been alleged by a number of recent workers, but the evidence for these does not meet the criteria laid down by such careful workers on cardio-dynamics as Frank, Hofmann, Straub or Wiggers. Gaskell's old observation that acid perfusion led to diastolic relaxation may have real physiological significance if it can be shown that the result is not secondary to variations induced in the phases of the regular systoles. Contraction remainder may well play an important part in diastolic filling as Henderson believes, but we do not feel it should be regarded as an example of tonus. Neither in our opinion, though its existence remains unproved, should the old physiological conception of the word tonus be usurped by such a definition as that proposed by Starling, one having to do not with a sustained contraction but with the available contractile power. Contractures while offering possible points of attack on the nature of muscular contraction have little or nothing to do with tonus. To conclude, whatever may be disclosed in the future, there is as yet no convincing experimental evidence that any kind of a sustained contraction persists throughout diastole which is subject to physiological modification.

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CURRENT VIEWS ON "INTERNAL SECRETION"

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A. INTRODUCTION. The term "internal secretion" has been put in inverted commas for the reason that many topics discussed in this paper have nothing whatever to do with secretion, either external or internal. They are, however, usually treated in books on the subject, and perhaps for the time being there is no more suitable place for their discussion. Again, many of those activities which are usually conceded to be of the general nature of internal secretion are so different in their mechanism from ordinary or external secretion that it is doubtful whether they ought to be included in the same category. If we compare our knowledge of the functional activities for example of the thyroid with those of the submaxillary gland, we see at once that the processes in the former are of quite a different nature from those in the latter. The fundamental difference between "glands" and "secretions" on the one hand and "ductless glands" and "internal secretions" on the other, was pointed out by the late Sir William Bayliss in a review of a book by the present writer. Bayliss wrote:

> The name "gland" implies to the physiologist many organs and tissues which have functions other than that of producing substances for the purpose of exerting a particular action on other organs or tissues when they pass into the blood-current. Those which form saliva and also the lymphatic glands may be mentioned. It is true that we might define a gland in a new way and say that any organ that produces some substance not already contained in the blood is entitled to the name. It would conduce to accuracy, however, if the name "gland" were limited to those organs able to pour out a secretion which can be collected and examined—those of "external secretion" in fact. In this case the ductless "glands" would have to be called "bodies" or some similar name, as is indeed frequently done in speaking of the "pituitary body" or the "suprarenal bodies." The name "secretion" itself as applied to the activity of the endocrine organs is also not very satisfactory.

Most physiologists will be prepared to admit that "secretion" and "internal secretion" are so different from each other that it is doubtful whether they ought both to be called "secretion." Confusion has

arisen from the fact that the term secretion has been applied to several different processes. As I have pointed out on previous occasions, the chemical processes of the manufacture of substances, the elaboration of these into a form suitable for elimination, the passage of water and other materials out of the secretory cell into the duct of the gland and the final expulsion of the product on to a free surface—all these are referred to as "secretion." If we make our definition of secretion to include all these things, then it is clear that what is commonly called "internal secretion" must be placed in a quite different category. We may also urge with Bayliss that the structures which carry out the process should be called "bodies" and not "glands." But Bayliss offered no suggestion as to what the process is to be called. The products he called "hormones" or "chemical messengers." This will be referred to again under the heading of nomenclature.

Bayliss' suggestion that "we might define a gland in a new way" has actually been carried out by many writers. The definition of a gland has been extended so as to apply to any structure (made up of cells of a special epithelial character) which forms a product—the secretion—which is discharged either upon a free epithelial surface, or upon the closed epithelial surface of the blood cavities. But it has been pointed out that the substances manufactured by the tissue should be of a highly specialized character, and not the ordinary products of metabolism, such as CO_2, lactic acid and urea.

B. DEFINITION AND LIMITATION OF THE TERM "INTERNAL SECRETION." Apart altogether from the difficult question as to whether the production of such substances as the active principles of the thyroid or the pituitary ought to be regarded as a process of true secretion, we have to discuss whether the presence in the tissues generally or the extraction from them of principles having distinct pharmacodynamical properties is necessarily to be regarded as evidence that the tissues furnish an internal secretion.

When it was found that by some of the methods employed to extract and test the physiological properties of the adrenals and the pituitary, active substances could be obtained from many different kinds of organs and tissues, the belief gained ground that the old morphological and physiological distinction between glands and other tissues should be set aside and the assumption was made that all the tissues of the body are capable of furnishing internal secretions, regardless altogether of their origin and histological structure. This view has been strenuously opposed from the morphological standpoint by Kohn. In one of his most

recent contributions on this subject (68), he discusses the claim of CO_2 to rank as an internal secretion. If, as he points out, the materials are called by some such name as "hormones" (vide infra, p. 296) no objection can be made, unless it be implied or definitely stated that the "hormones" are always the products of an act of secretion. The chemical coördination of body functions is an important subject and "internal secretion" is only a part of it. If the substances poured into the blood stream are manufactured in a specially constructed organ made up of highly specialized epithelial "secretory" cells, then we may perhaps, with the mental reserve indicated above, refer to a process of true secretion. If, on the other hand, the substance in question is an ordinary metabolic product such as CO_2, urea, lactic acid, etc., then the use of the term secretion is totally inadmissible.

Kohn also points out the confusion which has arisen by including the products of absorption from the alimentary canal as internal secretions. To refer to proteins, fat and sugar as internal secretions is inaccurate. Absorption is not an act of secretion and foodstuffs are not secretions.

C. Methods of study of "internal secretion." *1. The injection of extracts.* Space will not allow of the discussion of all the methods employed in the study of autacoid actions whether secretory or not. There is, however, one method which has been so extensively used and has been so fertile both in important facts and in groundless hypotheses, that we must make reference to it in this place. The method in question is the injection of extracts made in various ways from the different organs and tissues of the body. The technique was not much employed till Schäfer, working in conjunction with Oliver (80), discovered that extracts made from the adrenal bodies give rise (when injected into the veins of an animal) to a very great rise in the arterial blood pressure. It is worthy of note that all the fundamental facts in the whole subject were noted by Schäfer in these early papers. In his work with Oliver he observed that one other gland extract besides that of the adrenal, viz., the pituitary, contained a pressor principle, and in conjunction with Moore (87) he recorded that brain extracts produce a fall of blood pressure.

It gradually became clear that the rise of blood pressure given by adrenal and pituitary extracts was a very special result peculiar to these two organs, but that the fall of pressure first observed in the case of brain extract is a phenomenon obtained with extracts made from all kinds of organs and tissues (98). Although this was fully realized by workers conversant with the subject, yet from time to time papers have

appeared from authors who carefully described the depressor action of this or that tissue. Among recent examples are those of McDonald (75) and James, Laughton and Macallum (64) who have recently made the observation that extracts of liver have the power of lowering the blood pressure.

The nature of the depressor substance or substances in tissue extracts is not known. It was shown by Osborne and Vincent and by Vincent and Sheen (98) that the depressor effect of the nervous tissue extracts could not be attributable to choline, since a marked fall is obtainable in atropinized animals, while with choline in such animals there is always a rise. The same is true for tissues generally. Histamine has been suggested as a likely substance; and quite recently the idea has gained ground that the effect might be due to a mixture of choline and histamine in the extracts. It is, however, not difficult to show that there must be present some substance having totally different properties from either of these (97).

It has been pointed out on numerous occasions that these results are merely pharmacodynamical and bear no necessary relation to any hypothetical internal secretion or even production of "autacoid" substance by the tissues explored. In the case of the majority of tissues at any rate there is no reason to regard the presence of such active substances as evidence that the tissues in question furnish an internal secretion. It would for example be preposterous to assert that the presence of depressor substances in brain extracts has any direct bearing upon the problems of brain physiology. There is in this case not the slightest reason to suspect that the substances in question are "internal secretions," "autacoid substances" or anything of the kind. The whole line of investigation derived from the action of extracts has been carried out with a sad lack of critical judgment. Certain French writers (see 95) divide the glands of the body into two groups, "hypertensive" and "hypotensive," according to the action of their extracts upon the arterial blood pressure. Such a classification would put the chromaphil tissues and the nervous portion of the pituitary body into the first group, and all the other organs and tissues of the body into the second. The view is widely held that all organs and tissues of the body furnish internal secretions, and that the normal blood pressure and other standard conditions are maintained by a series of antagonistic chemical agencies arriving from different glands and tissues.

It is just as necessary today as it was some years ago to lay great stress on the fact that many if not most of the results obtained by the study

of the action of tissue extracts are of purely pharmacodynamical interest. It seems urgent to point out in the first place that the physiologically active substances found in extracts may not have been present in the living or even in the dead tissue, but were possibly produced by the manipulations mechanical and chemical employed in making the extracts. (See below, methods of preparing extracts, p. 301). Two further assumptions are often made, viz. that the substances in the extract are normally poured out into the blood stream to minister to the needs of the economy and that such pouring out is the result of an act of secretion. It is necessary to point out that each of these assumptions may be groundless.

2. Actions on isolated preparations. Another method which has had, and still has, a great vogue, is the testing of tissue extracts upon isolated preparations of smooth muscle, especially that of the uterus. It is particularly in connection with the study of the pituitary body that this technique calls most for comment. The favorite preparation is the isolated uterus of the virgin guinea pig. It is well known that the contractions of such a uterus are markedly increased by the addition of pituitary extract to the bath of Ringer-Locke solution in which the tissue is immersed. It is frequently assumed that a similar activity on the part of any tissue extract is evidence of the presence of a product of pituitary secretion.

In 1923 Dixon (33) injected extracts of organs into dogs and studied the effect on the pituitary body by estimating the amount of the uterus-contracting principle in the spinal fluid. A certain volume of spinal fluid was added to the uterus in Locke's fluid and the effect upon its contraction compared with that of a standard pituitrin solution. Dixon got no effects from extracts of liver, brain, choroid plexus, testis, epididymis, anterior lobe pituitary, thyroid and pancreas. Extracts from the interstitial portion of the ovary (i.e., ovary from which the corpus luteum had been removed) were the only ones which gave positive results. Two or three minutes after the injection of such extracts, there was demonstrable in the spinal fluid a considerable increase in the uterus-contracting principle which, it was assumed, must have been derived from the posterior lobe of the pituitary body. From these results Dixon came to the conclusion that extracts from the interstitial tissue of the ovary specifically excite the pituitary gland to secrete. "The facts seem clear," says Dixon, "that ovarian conditions determine the secretion of the pituitary, and thus react indirectly on the uterine tonus. Pituitrin is very largely employed in medicine to contract the

uterus: its employment would seem to be so far rational that it is the drug manufactured by the body for this specific purpose."[1]

A little later Dixon and Marshall (34) reported that ovaries containing corpora lutea were devoid of any influence on pituitary secretion, while the yellow bodies were fully active. As these underwent gradual retrogression, the power of the ovary to stimulate the pituitary simultaneously and proportionately increased. The authors considered that the corpus luteum so dominates the ovarian metabolism during pregnancy as to inhibit the normal ovarian secretion, but with the involution of the corpus luteum at the close of pregnancy the uterus shows an increasing irritability, and eventually, when the normal ovarian endocrine mechanism is sufficiently reëstablished, the secretion, working through the intermediation of the pituitary, becomes an important factor in bringing about labour.

These two papers are glaring examples of the fascinating theories which may be constructed if once doubtful data become accepted as true. In the first place it is by no means proven that the active substance of the pituitary body is carried into the blood through the spinal fluid. Again, it is a matter for serious discussion whether any uterus-contracting principle which may be found in the spinal fluid has any relation to the pituitary body. Further, blood and inflammatory products may cause a contraction of the guinea-pig uterus, and these may easily contaminate the spinal fluid used for experiment. But the most serious criticism of the work of Dixon and of Dixon and Marshall is to be found in a recent communication by Blau and Hancher (14) who have been quite unable to confirm the experimental results. (See also 67.) The isolated smooth muscle method is extremely delicate, and this fact renders it necessary that workers who employ it should be very critical of any results obtained.

D. CHEMICAL REGULATORS WHICH ARE NOT "INTERNAL SECRETIONS." A great deal of work has been done on "chemical regulators" apart altogether from any question of "internal secretion." Sharpey-Schafer (89) says that evidence is accumulating that special autacoid substances may be produced as the result of stimulation of efferent nerves: such autacoids may assist or prolong the effect caused by stimulation of the nerve. Thus it has been found that stimulation of the vagus or of the sympathetic fibers leading to the heart provokes the appearance of

[1] As has been pointed out on several occasions, it is difficult, on this assumption, to explain the occurrence of the substance in male animals.

chemical substances in the auricle, which, when applied by perfusion to another heart, cause either inhibition or weakening, or acceleration and augmentation of the beat according to whether the vagus or the sympathetic fibres of the first heart were stimulated. Similarly it has been found that the contraction of both skeletal and of plain muscle is accompanied by the production of autacoid substances—in the latter case possibly cholin—which may themselves cause a prolongation of the contractions. The authors quoted as supporting this view are O. Loewi (71, 72, 73), Geiger and Loewi (43), Brinkman and van Dam (16), L. Jendrassik (65), Ten Cate (93), H. Fredericq (42), and Brinkman and Ruiter (17).

On the other hand, L. Asher (5), J. F. and C. Heymans (59), E. and P. Gley (44) and others have obtained negative results.

An autacoid substance which is concerned with heart movements has been described by Haberlandt (46, 47, 48, 49, 50). This worker states that his substance is something quite different from Loewi's "Acceleransubstanz" and is obtained by alcoholic extraction of heart muscle or from Ringer's fluid in which pieces of heart muscle have been allowed to continue beating for some time. The substance has the effect of increasing the force and frequency of the heart beat, or even of starting the beats once more after they have ceased for a long time.

It is too early to come to any definite conclusion as to the significance of all this work. Here, as in other problems, it is difficult to distinguish between pharmacodynamical and physiological phenomena. In the case of many of the papers a doubt arises as to the number and adequacy of the control experiments.

A kind of pathological autacoid has been described. It is said that the blood of patients suffering from high blood pressure contains a substance which when injected into rabbits will raise their blood pressure (30). Curtis, Moncreiff and Wright, working in my laboratory, have found it impossible to confirm this (28).

Lewis (70) has urged the claims of histamine or some "histamine-like" substance to rank as a "chemical regulator" or an "autacoid." He reports that when a solution of histamine is punctured into the skin it gives rise to 1, a local dilatation of the capillaries, venules and arterioles by direct action; 2, a widespread dilatation of surrounding arterioles, resulting from a local axon reflex, and 3, a locally increased permeability of the walls of minute blood vessels by direct action. This total reaction is termed the "type reaction" and leads to local edema of the skin. The vascular reactions of the skin to stroking, scratching or burning are identical with those of the type reaction. Lewis concludes that the

reactions result from the liberation of a chemical substance in the skin, this substance having a "histamine-like" action on the blood vessels and nerves.

Burn and Dale (19, 20) report that when the general arterial pressure of a spinal preparation has fallen to a low level, through failing efficiency of the spinal vasomotor centres, injection of a small dose of histamine still causes a definite, though often relatively trivial, further fall of the arterial pressure. This fall, however, is frequently followed by a secondary rise of the pressure, which may be very considerable. The secondary rise does not occur if the adrenal bodies be extirpated. Burn and Dale also find that the effect of adrenin in small doses is a small primary pressor effect followed by a more considerable depressor effect. They conclude that there is evidence that a secondary pressor effect of histamine is due to accelerated output of adrenin, and that the depressor effect of small doses of adrenin is also a secondary effect, due to liberation of a "histamine-like principle." (See, however, 74 and discussion on p. 315.) The authors put forward some evidence which seems to point to the lungs in particular as a source of the "histamine-like" antagonist to adrenin. Capillary tone, on this theory, is under the balanced chemical control of adrenin on the one hand and this "histamine-like" substance on the other.[2]

Le Heux (56, 57, 58) has put forward the theory that choline is to be regarded as the autacoid substance of gastro-intestinal motility, and the view is supported by Abderhalden and Paffrath (1). Mulinos (79), on the other hand, is unable to confirm the statements on which the theory is based.

E. NOMENCLATURE. A survey of the nomenclature of internal secretion and other processes of chemical regulation may be of value, not only because the words coined for things or processes are a reflection of current views, but also for the reason that the words, once they become current, play a large part in moulding the ideas of teachers and learners.

By the older writers the "*consensus partium*" was supposed to depend on the nervous system. The modern "Syzygiology" (σύζυγος, yoked together) is supported largely by chemical considerations (99). The doctrine of internal secretion as it is taught today was founded by Claude Bernard (9) and Brown-Séquard (18). Bernard (9) stated in very explicit terms that certain organs, such as the spleen, the thyroid

[2] Since the above was written Dale has, I believe, abandoned the theory in question.

body, the suprarenal capsules and the lymphatic glands, furnish an *internal secretion.*

In 1905 Starling introduced the word "*hormone*" (ὁρμάω, to stir up, arouse, or excite). The word soon came into general use and was commonly employed as synonymous with "internal secretion," though it was defined as meaning a "*chemical messenger.*" Now the word itself implies neither a chemical nature nor a messenger's duties. As pointed out by Sharpey-Schafer, the expression "*hermone*" (Ἑρμης, Mercury) might have been used if the intention had been to convey the idea of a messenger. But as I have indicated on previous occasions it is not clear that we need a word to mean "chemical messenger." The substances poured into the blood-stream by the organs of internal secretion do not deliver a message and then return to their central office. In many cases they stay where they are sent and perform the functions of workman, agitator, policeman or drug. As pointed out by Hoskins, the term hormone has little more than usage[3] to commend it. The word means an excitor but various substances called by this name actually depress bodily functions.

In 1911 Gley introduced the term "*harmozone*" (ἁρμόζω, I govern or regulate) to apply to substances which regulate chemical processes and functions. The harmozones are further divided by him into three groups: 1, helping in nutritive exchanges; 2, serving to maintain the composition of the blood and lymph; and 3, having a morphogenetic function. According to Gley, Starling's term "hormone" should be retained for specific functional excitants. Gley has also recommended another word *parhormone*, to be used for such substances as CO_2, which he considers not to be true hormones but waste products having an accessory excitatory rôle. It is probable that the action of CO_2 on the respiratory centre may be regarded as a simple pH change, which could scarcely be called a "hormone."

When it became recognized that the "internal secretions" (or chemical regulators which are not internal secretions) do not all act as excitants (vide supra) the need for new nomenclature was felt. As a result, in 1913 Sharpey-Schafer suggested two new terms. The word "hormone" he points out, should be restricted to excitor secretions, while for those with inhibitory or relaxing actions he would use the word "*chalone*" (χαλάω, to make slack or relax). For an expression to include both *hormones* and *chalones* Sharpey-Schafer advises the term "*autacoid substance*" (ἀκος, a remedy, and ἀυτος, self), to denote any drug-like prin-

[3] And, it may be admitted, a certain euphony.

ciple produced in or extracted from the organs and tissues of the body. So that we have, according to Sharpey-Schafer the "*autacoid substances,*" divided into two groups, *hormones* or excitants, and *chalones* or depressants. The introduction of these terms and the classification involved, while it appears to remove an obvious objection to the original use of the term "hormone", has not improved the situation very materially. The term "hormone" will now appear in the literature employed in two different senses, and would have an ambiguous significance depending on whether the newer or the older usage were understood. But the most serious objection to Sharpey-Schafer's classification is one which was pointed out by himself, namely, that it is not feasible to classify "chemical regulators"[4] as exciting or depressing. Thus adrenin excites some tissues while it depresses others. For example, in small doses it causes the skin vessels to constrict while those of the underlying muscles dilate. Again, the effect of adrenin on certain tissues may be either excitation or depression, according to the dosage. Thus, although moderate concentration of adrenin passed through the blood-vessels of skeletal muscles causes augmented venous outflow, larger quantities result in a diminished flow. A similar reversal of effect with change of dosage has been reported in the lungs (Hoskins, 62).

As Hoskins points out, the attempt to meet the difficulty by the assumption that the process is actually excitation in each instance—in the one case augmenting, and in the other depressing mechanisms being involved—merely raises the question as to the nature of inhibition.

Hoskins thinks that the word autacoid is hardly a happy selection, for the word drug connotes a foreign substance, whereas internal secretions are precisely the opposite. But this criticism surely overlooks the "aut'" part of the word which implies "self." If the term be used to mean a drug formed in the body, there is no objection to it; indeed, it seems to me that it is the best which has been proposed. The drug-like bodies or chemical regulators may be appropriately referred to as "autacoid substances" or "autacoids."[5] Only some of these could be

[4] I have here, as in some other places, used this expression where originally "internal secretion" would be used. The explanation is given above.

[5] I have before me an announcement of a joint meeting of the Biochemical Society and the London Section of the Society of Chemical Industry to discuss "The scientific and industrial problems presented by the hormones, the natural drugs of the body." If the intention was to describe "natural drugs," it is a pity the term "autacoid" could not have been used, since the word was coined by Sharpey-Schafer for this purpose. The term "hormones" as explained above does not imply "the natural drugs of the body" but simply the idea of some kind of stimulators or excitors.

called "internal secretions," namely, those which are the products of a specialized "epithelial," "glandular" organ or tissue.

The same kind of criticism as was offered to the terms "hormone" and "chalone" applies of course to any attempt to classify autacoid substances into "hypertensive "and "hypotensive." The uncritical use of the method of extracts led Livon to divide the glands of the body into two groups, according as their extracts cause a rise or a fall of blood-pressure when injected into the veins of an animal. Other writers hold similar views. If we insist on making such a classification, it follows that we have to place the chromaphil tissues and the nervous portion of the pituitary in the first group, and all the other organs and tissues of the body in the second group. Moreover, as we have seen, the chromaphil tissues furnish a substance which in small doses is hypotensive while in larger doses it is hypertensive.[6]

The word *endocrine* is very generally employed as an adjective applied to internally secreting organs, their functions, and their products, and in antithesis to *exocrine*. Among a certain number of American writers "endocrine" has been made into a substantive and we frequently hear or read of the "endocrines" as a generic term to include all the organs of internal secretion, or the products of the manufacturing druggists.

Matthews has made use of the expression "*cryptorhetic*" (κρυπτός, hidden, and ῥέω, to flow) as applying to the structures furnishing internal secretions. The term has the advantage of being non-committal in respect of any theory as to the way in which the substances are produced or in which they act. It is in this respect better than "endocrine" (Ἔνδον within, and κρινω, to separate) or "internal secretion" for both these terms imply some kind of "secretion." "*Incretion*" is now frequently used. If its antithesis "excretion" be used it would mean ordinary secretion. Noël Paton (82) considers that our present terminology is at fault because it does not correspond to the most reasonable view of the mode of action of the substances we are considering. He thinks that the "internal secretions"[7] play a part similar to that of the salts of the blood in maintaining the efficiency of the heart's action. "A certain minimum amount of each seems to be essential, and some proportion between the amounts of each must be maintained if the metabolism is to continue in its normal course . . . . . Such a concep-

[6] See, however, pp. 314–315.

[7] And by this term it is supposed he would include autacoid substances which are not secretions.

tion is more in accordance with the facts which we possess than that of a series of hormones or excitors calling forth the activity of the various tissues." This mode of presentation would agree fairly well with what we know of the part played by the active principle of the thyroid body in relation to the metabolism of the organism. Paton does not say definitely that the internal secretions or autacoid substances act as catalytic agents, though other authors have not been so careful (52). As Starling (91) points out we should not speak of catalysis—i.e., a hastening of a chemical action—unless we have some definite chemical action in mind. "In the case of these hormones, as in the case of drugs such as alkaloids, we have not the remotest idea how they work. It may be that their action is by catalysis of one or other of the reactions which occur in the series making up the life of the cell, but there is no evidence for or against such a statement, and there is a distinct danger that by putting the action of drugs or hormones into such a category, we may forget our ignorance and refrain from further attempts at an analysis of the manner in which they work" (91).

The terminolgy of organs and tissues concerned in, or supposed to be concerned in, the formation of internal secretions, is still somewhat chaotic. Wherever the writer is persuaded that the organ in question is in truth engaged in this function, there is a tendency to call it a "gland," rather than simply a "body," a "nodule," a "corpuscle," or what not. Thus, in place of the old "suprarenal capsule" the modern tendency is to refer to the "suprarenal or adrenal gland." The same applies to the thyroid, parathyroids and pituitary. The danger is that having once called a structure a gland, the assumption that it secretes is often made without sufficient evidence. This has been the case with several structures, such as the lymph nodes and the thymus. The term "*ductless glands*" is still sometimes used, but is not quite satisfactory, because it excludes certain of the glands with ducts which are generally admitted to furnish both external and internal secretions, as in the case of the pancreas.[8]

The nomenclature of the individual organs varies very considerably among different writers. The adrenal gland or body is usually divided into a *cortex and medulla*, and these terms are useful, nay, necessary in

[8] Here, it is true that many people would maintain that the "ductless glands" of the pancreas, which supply the internal secretion, are the "islets of Langerhans." Many also would hold, on a much slighter basis of evidence, that in the reproductive organs, the "ductless gland" is made up of the interstitial cells.

everyday work, but punctilious writers are only doing their duty when they remind us that the term adrenal gland should be applied to the "cortex" and that the "medulla" is simply a collection of "*chromaphil cells*" which has insinuated itself into the adrenal gland or body. The cortex is frequently referred to as the "interrenal" gland, organ or body, because its homologue in elasmobranch fishes is placed between the two halves of the kidney. What I have referred to as "chromaphil" cells, are perhaps more frequently called "chromaffin." The former term is the more desirable because it is nearer to Stilling's original "chromophil." "Chromaffin" was quite unnecessarily introduced by Kohn. All that was needful was to alter the "o" to "a" and make the word "chroma*a*phil" instead of "chrom*o*phil", which of course means simply "deeply staining."

The terminology applied to the active principles, the "autacoid substances" themselves, is very confused. For the substance extracted from the chromaphil tissues there are names without end. Among the older and better known are "*epinephrin,*" "*sphygmogenin,*" "*adrenalin,*" "*hemisin,*" "*paraganglin*" and "*myosthenin.*" "*Adrenalin,*" however, is the term most commonly used; but it is obviously an advantage to adopt a name which has no commercial attachments and Sharpey-Schafer suggests "*adrenin.*" This term should be used whenever reference is made to the substance as a chemical entity and not to some particular commercial preparation. To designate the pure active substance of the thyroid, Kendall introduced the name "*thyroxin,*" which has been widely adopted. The active constituents of the pituitary body are called by various names,—"*pituitrin,*" "*hypophysin,*" "*tethelin,*" etc. The active principle or principles have not yet been obtained in a pure form. "*Spermin*" is often used for the autacoid substance of the testis, but it seems clear that the nitrogenous body to which this name was given has little or no relation to the actual "internal secretion" of the testicle. *Oestrin* has recently come into use.

The name "*insulin*" was first applied to the autacoid substance of the pancreas by de Meyer (77) in 1909, and the word was later independently used by Sharpey-Schafer (89) in 1916, and by the Toronto workers in 1922.

There are many Greek-Latin hybrids in common use, and to these Hoskins rightly takes exception. But it is much more important to see to it that the words in their philological structure and obvious meaning should correspond with the most approved notions as to their nature and activities.

F. METHODS OF PREPARING EXTRACTS OF ORGANS AND TISSUES. This subject is very complicated from every standpoint. So far as I am aware there has been no previous attempt to review the whole ground in its more general aspects. There can be little doubt that many of the preparations which are in general use for medicinal purposes are quite inactive and this even where by proper methods powerful principles may be prepared. A difficulty which faces us at the outset consists in deciding whether a pharmacodynamical effect is due to a substance originally occurring in the tissue or whether it is result of some change arising from the physical and chemical manipulations employed in the making of the extract. Even if the latter be the case, it is not impossible that the substance formed might be normally produced in the body by processes of a different nature. This question is of course quite separate from that which concerns itself with the autacoid or secretory nature of the material.

Many of the earlier investigations upon tissue extract were carried out with the adrenal bodies. Before the discovery of Oliver and Schäfer, Pellacani (83), both alone and in conjunction with Foa (84), had used filtered aqueous extract of fresh adrenal body, and had administered this subcutaneously. Oliver and Schäfer employed extracts of the adrenal bodies prepared with water, with alcohol of various strengths, and with glycerine. They were made either by digesting an ascertained weight of the fresh gland or of the dried gland in these menstrua, or, in addition, by boiling the infusion for a few minutes. When an extract made with alcohol or with glycerine was injected it was diluted with water or salt solution and an equivalent amount of alcohol and glycerine diluted with water to the same extent was injected into the animal as a control. Extracts were also prepared with absolute alcohol, ether, nigroin, and various other solvents. These were evaporated to dryness and the residue was either dissolved or suspended in water or salt solution and thus injected. Oliver and Schäfer observed that with alcohol and ether absolutely free from water no active principle whatever was extracted by those fluids provided that perfectly dehydrated gland substance was used. The presence of a small amount of water in the alcohol or the water which enters into the composition of the normal fresh gland was sufficient to enable the alcohol to take up a certain amount of active material. Care was always taken to employ solutions which had been filtered free from all obvious particles.

A method very frequently employed and consisting in only a slight modification of the principal method of Oliver and Schäfer is that of

"saline decoctions". The tissue is chopped fine or passed through a mincing machine, ground up in a mortar with sand or powdered glass and the result diluted with normal saline solution. The fluid is momentarily raised to the boiling point and a drop or two of acetic acid added. It is then passed through a filter paper in the ordinary way.

Such a saline decoction contains some protein, although the greater part may have been removed by the boiling in an acid medium. Proteoses and peptones are also present. In the case of many tissues, if not in all, choline and histamine can be found in the saline decoction. There are, of course, large numbers of other substances, among which one or more have a depressor action. The extracts prepared in this way should always be re-filtered before use, especially if any particles become visible. Filtering through a Chamberland filter is very desirable. Observations on the filtration of insulin have shown that the reaction of the fluid must be well removed from the iso-electric point of the active principle. It is usually safe to adjust the reaction to the acid side, i.e., pH 3. Shaking with benzene will get rid of the phosphatides and render the preparation less liable to cause clotting of blood. A saline decoction of the appropriate tissue will contain adrenin, secretin, and the active principles of the thyroid and pituitary bodies.

Brown-Séquard (18) prepared his famous testicular extracts by the simple process of cutting the tissue into small pieces, pounding in a mortar, adding water and filtering. This last process, of course, he found very difficult and the filtrate was turbid or opalescent and pinkish in colour. The preparation was a "protein extract" and would have been dangerous if intravenously injected.

Such acid, watery, or saline decoctions, if prepared from the duodenal mucous membrane, will be found to contain secretin. Bayliss and Starling (7) used hydrochloric acid and in such quantities that the extract had to be neutralized before injection. Dale and Laidlaw (29) ground up the mucous membrane with mercuric chloride. Two cubic centimeters of water were added for each gram of tissue. The mixture was then boiled and filtered, the filtrate being rejected. The solid matter was then dried and placed in a solution consisting of 2 per cent acetic acid and 1 per cent mercuric chloride. After boiling and filtering, 10 per cent sodium hydroxide was added to neutralization, judged by the fact that the yellow precipitate of mercuric oxide would just not remain permanent. On standing, a precipitate of a mercury compound of secretin fell down. This was suspended in water and freed from Hg by means of hydrogen sulphide. The insoluble mercuric sulphide was

filtered off and the solution was neutralized. After boiling off the sulphuretted hydrogen, a strongly active solution was obtained. Picric acid will also precipitate the active principle. Various other methods may be employed. The amount of secretin produced seems to be independent of any particular acid radicle. Secretin may also be extracted by alcohol, strong soap solutions, or sodium chloride. It is said that a powerful secretin preparation may be prepared by precipitating secretin solutions by means of acetone. Mellanby (76) has recently used a method in which the secretin is extracted by absolute alcohol and absorbed by bile salts. It would appear that preparations made in this way are more active than those prepared by the methods just described.

A saline decoction of pancreas prepared as described above will be found to contain a certain amount of insulin. But the methods which have been employed for the clinical and commercial products are very numerous. Alcohol, water, acetone, are used as solvents, benzoic acid to carry down the insulin when it is precipitated, ammonium sulphate to precipitate the active substance. Both acid and alkaline processes are employed for extraction.

Among the aqueous methods that of Dodds and Dickens (35, 36) deserves special mention, as its application has so materially reduced the cost of production. This method depends upon the fact that these workers were the first to observe that insulin picrate is soluble in 70 per cent aqueous acetone, whereas the inactive picrates are insoluble. Owing to the difficulties attending aqueous extraction, picric acid is applied directly to the tissues, which are then extracted with acetone. The pancreas is minced and stirred with powdered picric acid. The picrate is then extracted with acetone, filtered, and the filtrate distilled in vacuo at about 50°C. until all the acetone is removed. From the aqueous residue a deposit of the amorphous precipitate of the picrate separates. This is now converted into the hydrochloride by dissolving in acid alcohol and precipitating by acetone. It is then washed with acetone and ether and then dried in a vacuum desiccator.

If the autacoid substance provided by an organ or tissue be present in lipoid form or in lipoid combination, the preceding methods will not serve to extract it, or at any rate will not be most suitable for this purpose. This applies to the active principle of the ovary, and probably to those of the testis, the corpus luteum, the adrenal cortex and others.

In regard to the ovary, it is curious that some of the earlier work seemed to show that the substance which gives rise to oestrus may be present in aqueous extracts. In the year 1902 the present writer, in

conjunction with Dr. F. H. A. Marshall, observed slight signs of the oestrous condition after subcutaneous injections of aqueous decoction of ovary. Since then Marshall and Jolly have reported that "heat" or a transient condition resembling it can be produced by the injection of aqueous decoction of oestrous ovaries. The changes brought about do not seem to have been true cyclic growth processes, but simply transient circulatory effects. In 1912 Adler (3) reported the production of artificial oestrus in animals by the injection of aqueous extracts of ovaries.

In 1912 also Iscovesco (63) extracted ovaries with alcohol and obtained a fatty substance which he reported to contain the active principle. This work has been greatly advertised commercially in France. Fellner (41) showed that the active principle is thermostable and soluble in alcohol, ether and acetone. Similar results have been obtained by several workers, notably by Hermann and Fränkel (54, 55). These workers extract with alcohol, filter, and the filtrate is evaporated to dryness. The residue is extracted with ether, and acetone is added to precipitate the lipoid. The active principle remains after the solvent has been removed by distillation. As much cholesterol as possible is separated from it by fractional crystallisation, and the material is distilled *in vacuo* at 190°C.

But the discovery by Stockard and Papanicolaou (92) that a vaginal smear may be used as a test of the precise oestrous condition of the animal, opened a new chapter in the history of the subject. Allen and Doisy (4) used a method which did not differ materially from that of Herrmann and Fränkel, but they employed the vaginal smear method of determining the actual onset of oestrus. They appear to be of the opinion that the active principle is found mainly in the liquor folliculi.

Dickens, Dodds and Wright (32) have employed a slight modification of the method of Herrmann and Fränkel (employed also by Allen and Doisy). Pigs' ovaries are extracted with alcohol. After stirring, the mixture is pressed out in a hand press through jean, and the solid material is then extracted in a Soxhlet apparatus with alcohol for 6 to 9 hours. The alcoholic extracts are then combined and filtered. The filtrate is evaporated almost to dryness in vacuo and the residue is taken up in a small volume of alcohol and filtered. On standing, a precipitate of fats and cholesterol separates. This is removed by filtration. The solution is again evaporated to dryness, and the residue dissolved in a small quantity of ether, and twice its volume of acetone is added. The precipitated lipins are filtered off. The solid material is then redis-

solved in ether and again precipitated with acetone. This process is repeated several times. The filtrates are then combined, and evaporated to dryness. The residue is dissolved in a small quantity of alcohol, and some cholesterol is removed by freezing. By repeating this process, the greater part of the cholesterol can be removed. The final product is obtained by distilling off the alcohol *in vacuo*.

In conformity with the results of the earlier workers (vide supra), Dickens, Dodds and Wright obtained a certain small amount of active substance from watery extracts. But they believe that this does not imply that the autacoid is soluble in water. It is only a kind of emulsion which is obtained at the beginning of the process. This would of course apply to the active extracts of the earlier workers.

Quite recently Ralls, Jordan and Doisy (85) have dispensed with the acetone precipitation of phospholipins and employ petroleum ether to get rid of cholesterol.

A method of the same type is employed by Robertson (86) for the extraction of "tethelin" from the anterior lobe of the pituitary body.

Stress has been laid upon the details of extraction of the active substances from the ovary, because the work is new and is typical of methods which are likely to be employed very largely in the future (see 81).

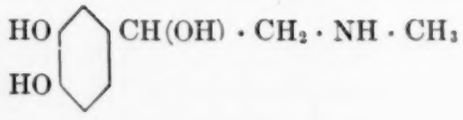
The autacoid substance of the parathyroid has claimed a great deal of attention within recent years. Collip and his co-workers (21, 22, 23, 24, 25, 26) have reported that the active principle may be extracted by digesting the glands with 5 per cent hydrochloric acid at 100°, and the product is obtained by a series of iso-electric precipitations from the digest fluid. When injected subcutaneously into dogs the serum calcium content can be raised. Collip was of the opinion that herbivorous animals are resistant to the parathyroid principle, but Davies, Dickens and Dodds (31) have found that a uniform rise in serum calcium can always be provoked in rabbits by the injection of suitable quantities. These observers consider that the specificity of the parathyroid autacoid substance remains to be proved, since they find that an extract made from pancreas by Collip and Clark's method gives marked rises in the serum calcium content. Insulin, and to a less extent, pituitrin, also raise the serum calcium content. Davies, Dickens and Dodds report that the active substance may be extracted from the parathyroid by means of the acetone picric acid process.

Exactly similar results were found when tissues other than the pancreas were extracted for insulin. Baker, Dickens and Dodds (6) studied the distribution of insulin in human cadavers, and found that even the

pancreas of a diabetic contained appreciable quantities of insulin. Best, Smith and Scott (13), working with depancreatised dogs, were able to demonstrate the presence of insulin in the muscles. These observations throw doubt upon the specificity of insulin as the internal secretion of the pancreas.

Krumbhaar (69) calls attention to the report of Hall and Ablahadian that the intravenous injection of a splenic extract into rabbits causes a marked rise in blood calcium, and states that his own work confirms this result "to a certain extent."

G. THE PREPARATION OF PURIFIED ACTIVE PRINCIPLES. If adrenin be actually the autacoid principle of the chromaphil tissues then the chemist has finished his work. The substance can be separated in crystalline form from the tissues or it can be synthesised. Its chemical constitution is



The fresh tissues are extracted with acidulated water (Takamine) or with alcohol (Abel), but the details of preparation must be sought in the original. (See also Dodds and Dickens (37).)

With regard to the active substance of the thyroid, we are not on such sure ground. The thyroid principle is only sparingly soluble in water, and the process employed by Kendall for the isolation of his "thyroxin" was hydrolysis by means of alcoholic sodium hydroxide. Kendall obtained only 33 grams of thyroxin from three tons of fresh gland. Harington (51, 52) found that hydrolysis with barium hydroxide gives better results, and yields 0.027 per cent of thyroxin. He holds different views also as to the chemistry of the active substance.

Starting with desiccated thyroid substance Harington subjects the material to a preliminary hydrolysis by boiling for some hours with 10 per cent solution of crystalline barium hydroxide. The solution is then filtered and the filtrate is acidified with hydrochloric acid and the precipitate (after dissolving in water with the aid of ammonia) is treated with 40 per cent crystalline barium hydroxide and subjected to a further hydrolysis. The solution is filtered hot and the precipitate ground up and suspended in 10 per cent sodium hydroxide. The solution is boiled and treated with sodium sulphate and filtered from barium sulphate. The filtrate is boiled and treated with sulphuric acid and the boiling is continued. The heavy precipitate is dissolved in sodium hydroxide,

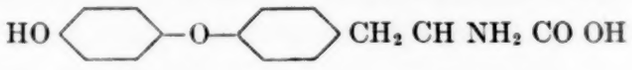
alcohol is added to about 80 per cent concentration, the solution is filtered from a small amount of tar, brought to the boil and treated with 10 cc. of 33 per cent acetic acid; thyroxin thereupon separates in a partially crystalline condition. The yield is about 0.12 per cent of the dried gland and the empirical formula is given as $C_{15}H_{11}O_4NI_4$.

As a means of investigating the chemical constitution of thyroxin, it is desirable first of all to get the substance free from iodine. This is achieved by the use of the palladium hydroxide-calcium carbonate catalyst of Busch and Stöve. On shaking a 1 per cent solution of thyroxin in N potassium hydroxide in an atmosphere of hydrogen with the catalyst the iodine is split off as potassium iodide and iodine free thyroxin (desiodo-thyroxin) is left behind.

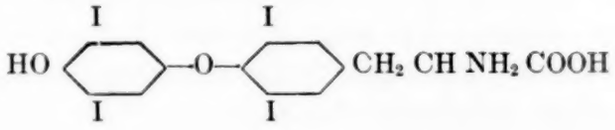
$$C_{15}\,H_{11}\,O_4\,NI_4 + 4\,H_2 = C_{15}\,H_{15}\,O_4\,N + 4HI$$

Desiodo-thyroxin.

Desiodo-thyroxin gives Millon's reaction and the ninhydrin reaction and yields the whole of its nitrogen with nitrous acid in Van Slyke's apparatus; it forms salts with acid and alkali; it is probably therefore an α-amino-acid with at least one phenolic group. On fusion with potassium hydroxide p-hydroxy-benzoic acid and quinol are formed, indicating the presence of two benzene rings. On exhaustive methylation, the product (betaine) loses trimethylamine, giving an unsaturated acid, $C_{16}H_{14}O_4$ containing one methoxyl group, proving the presence of one phenolic group only in desiodo-thyroxin. Further, the splitting off of oxalic acid by oxidation, with the formation of a residual stable acid suggests that desiodo-thyroxin may be a diphenyl ether of the structure.



This is the p-hydroxyphenyl ether of tyrosine. This formula is confirmed by synthesis and shows that thyroxin is a tetra-iodo substituted derivative of desiodo-thyroxin.



Harington and Barger have recently synthesized this substance from hydroquinone and tri-iodo-nitro-benzene. This product is indistinguishable from that isolated from the thyroid.

The bearing of all this on organo-therapy is sufficiently obvious. If the active principles are to be retained in the final product as sold by the druggist, it is clear that appropriate methods of extraction must be employed in each case. It is of importance also that care should be taken in the process of manufacture that the active principle or principles should not be destroyed by the chemical manipulations.

H. The interrelations of the organs of internal secretion. In no part of the subject of endocrinology is there a more striking disproportion between our certain knowledge of facts and the theories put forward than in that which deals with interrelations, yet the reader can scarcely open a medical journal without seeing some allusion to a relationship between the organs furnishing internal secretions. Among clinical workers who specialize in diseases of the "ductless glands" the belief seems to be almost universal that derangement of any one of the glands in question will lead to more or less evident disturbance in many or all of the others. The phrase "polyglandular syndrome" or "pluriglandular syndrome" is an everyday expression in modern medical literature. But the clinicians are not alone in this fashion of regarding the subject. Investigators in the fields of experimental physiology and pathology have been so impressed by cases where the autacoid substance of one organ affects the activity of another that many of them have joined with the clinicians in regarding the organs of internal secretion as forming a system whose several functions are very intimately related to each other.

It is, in fact, very remarkable that there has been so much talk about the interrelations of the organs of internal secretion. Nothing comparable in amount has been written or said about the "interrelations" of other organs in the body, even when they form a definite anatomical and physiological series, as, for example, is the case with the digestive organs. It is curious, however, that there is a tendency to repudiate any physiological relationship in cases where the different tissues are most intimately associated together. Thus, I imagine that the majority of writers insist that thyroid and parathyroid are totally separate and independent organs. The same applies to the adrenal (cortex) and the chromaphil tissues, and again to the secreting tubules and the islets of Langerhans of the pancreas.

It is difficult to understand exactly what kind of "system" could be constituted by a physiological association of the various organs and tissues which are, or which have been alleged to be, internally secretory. In some expositions of the subject the "system" is said to embrace not

only the adrenal bodies, the thyroid glands, and the pituitary, thymus, parathyroid and pineal, but also the reproductive organs, the pancreas, liver, spleen, duodenum, small intestines generally, the stomach, the uterus, and the mammary gland. According to other accounts, a "system" is made up of brain, thyroid, adrenal, liver, pancreas and muscles. It is commonly believed that the whole of the sympathetically innervated organs and tissues are under the control of the chromaphil tissues. It is alleged that the carbohydrate metabolism of the body is under the conjoint control of the central nervous system, the liver, the pancreas, the intestine, the chromaphil tissues, the thyroids and parathyroids, and the pituitary. Various other schemes of relationship have been suggested, so that it becomes impossible to form any concept of all the asserted possible relationships.

As I have pointed out on a previous occasion, a summary of the various connections just enumerated would amount to nothing more than an enunciation of the statement that the various organs and tissues of the body are functionally related to each other. It is not rare, however, to find an enthusiastic "endocrinologist" who believes that the organs of internal secretion dominate the whole of the bodily activities, normal and pathological, and are to be placed even above the nervous system in the hierarchy of organs. More than in any other branch of "endocrinology" there has been undue haste in formulating theories of interrelationships. Perhaps the clinicians have been on the whole greater offenders than the laboratory workers, and especially does this apply to the therapeutic application of theories of co-related disturbances.

Anyone who has approached the subject of internal secretion from the standpoint of comparative anatomy will look with grave suspicion on any theory which postulates that all the various internally secreting structures are specially related to each other, that they form a "system." From a morphological standpoint it is difficult or impossible to arrange all these structures in any kind of coherent series. There are many reasons for regarding the thyroid, parathyroids and thymus (along with certain less important branchial cleft organs) as morphologically related. Some authors regard the thymus as closely related to the thyroids and parathyroids from a physiological as well as a morphological standpoint. The glandular portions of the pituitary body may possibly be included in the same morphological group, but it must be remembered that the origin of the different organs mentioned is by no means identical. The only embryological feature common to all of them is that they arise

from some part of the primitive alimentary canal or its vascular outgrowths, the gill-clefts. The pituitary body arises from the ectoderm, while the branchial cleft organs are of entodermal origin.

In the region of the reproductive organs are found various types of "epithelial organ," notably the adrenal cortex. It has often been supposed that the corpus luteum and the "interstitial" cells of ovary and testis may belong to the same group. But, notwithstanding the enormous literature, the subject remains obscure.

According to the common view, the chromaphil tissues should be looked upon as glandular organs derived from the sympathetic nervous system and set apart to look after its interests. There is no space for a discussion of this subject. (See Vincent, 96.)

It is still a matter of doubt whether the adrenal bodies (cortex and medulla taken together) may justly be regarded as constituting functional entities. A large number of writers would decide in the affirmative, but if the evidence be carefully examined it will have to be conceded that, so far as is definitely known, the chromaphil tissues have physiologically nothing whatever to do with the adrenal system (or adrenal cortex and "accessory cortical bodies" (96)).

The pancreas, along with its islets of Langerhans, being an outgrowth from the alimentary canal, might be regarded as belonging to the same system as the branchial cleft organs.

But in all this discussion we must bear in mind that at the present time we have not sufficient knowledge of comparative physiology to inform us with any degree of authority in how far we are justified in regarding morphological and embryological connections as certain proof of physiological relation.

Most of the schemes of interrelationship which have been presented assume that the endocrine glands form a closed ring or triangle, and that the individual glands may be mutually antagonistic or helpful. A typical conception is that of Falta, Eppinger, Rudinger and Hess, which has been complicated and extended so as to include the pituitary body and the ovary.

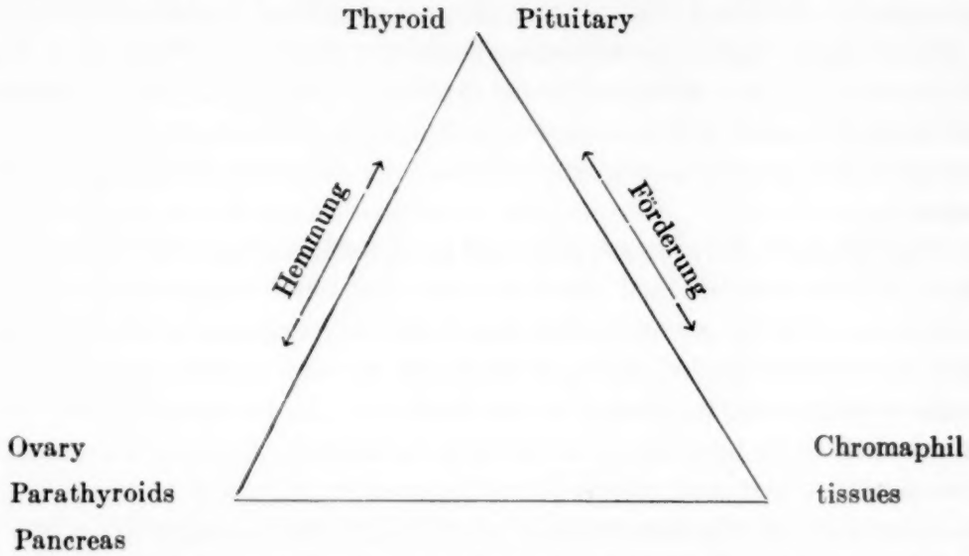
It seems clear that the actions of the autacoid substances on organs and structures other than those of internal secretion is a matter of very considerable importance. Those which act upon the nervous system will naturally exercise a far-reaching influence on the whole body.

Again an organ which modifies the circulation of the blood will affect the nutrition and functions of many parts. Further, any variations in general metabolism brought about by an organ will produce changes in

the whole organism. Such effects are probably of more potency than mutual actions of the various glands upon each other.

The changes produced in this way may be in the direction either of "Hemmung" or "Bahnung." Many examples will be found in the literature.

A scheme given by Weil (99) will serve as an example:



From the scheme the mutual interdependence of the glands would be shown, for example, by deficiency of the pituitary body, in which case the secretion of the ovaries would be increased, and, conversely, if the ovaries are deficient the secretion of the pituitary would be increased. It will be observed that no place is found for the adrenal body (the so-called "cortex") only for the chromaphil tissue. Again, a well-known relationship between thyroid and pituitary is not represented. If, indeed, all the known or suspected relations were embraced in a single diagram this would be too complicated to serve as a guide and would lead to hopeless confusion.

From the considerations outlined above it is clear that at the present time it is impossible to present any scheme of definite interrelationship between the various glands of internal secretion. The influence of the internal secretions on any organ or function depends not only on mutual actions of these secretions, but upon their action on various bodily functions, including the nervous activities and widespread chemical processes.

Notwithstanding what has been just said, it may be of some interest to consult a more circumstantial account of many of the various known

or alleged interrelations of the organs of internal secretion. The first authoritative summary of this subject was written by Hoskins (60) in 1911, and a later treatment by the same author was undertaken in 1922 (61). A still later compilation was made by Vincent in 1924 (96).

I. Methods of administration of autacoid substances. If one judged by the lists of endocrine products advertised by the druggists it would be imagined that all the physiological and therapeutic effects of the various organs and tissues could be produced when they are administered by the mouth. So far is this from the true state of affairs, that it may be said without much risk that none of them, except thyroid preparations, produce any appreciable effects when taken into the stomach.

Collip thought that his parathyroid preparations were effective when taken by the mouth, but this view has not been confirmed by other observers. Several physicians have reported changes in metabolism after administration of adrenal products in the same manner, and pituitary substance is often given in this way. But most observers are agreed that both pituitary and adrenal substance, to produce any effects, must be injected either beneath the skin or into a vein. Evans and Long (38, 39, 40) declare that the overgrowth produced by administration of anterior pituitary can only be observed when the substance is injected intraperitoneally. Many physicians continue to order ovarian substance to be taken by the mouth, though all the best evidence shows that this is useless and that ovarian material must be injected subcutaneously or intravenously.

The fact must not be overlooked that many of the commercial preparations of ovarian substance do not contain the active principle, and so the mode of administration can be of no import. The same is probably true of preparations of some other glands and tissues.

J. Some recent investigations on various autacoid substances. *1. Ovary.* Among the more notable achievements since the work of Banting and Best on insulin in 1922, is the preparation of an active extract from the ovary, as described in a previous section (pp. 303–304). The activity of the extract is manifested in its power of bringing about changes practically identical with those of oestrus. This observation would, it might be imagined, be sufficient to establish beyond a doubt the "internal secretion" theory of sex-organization, as opposed to an alternative metabolistic interpretation. But the consideration that a large yield of an autacoid substance, having a similar action to that from the ovary, may be obtained from the placenta, is very disturbing.

2. Insulin. The investigations of Dale and his co-workers have thrown some light on the mode of action of insulin.

The fate of the glucose which disappears from the blood after injection of insulin has been the subject of much experimentation. If an eviscerated spinal cat be employed, it can be shown that when glucose is circulated through the preparations, it disappears from the blood at a greater rate after administration of insulin (Burn and Dale, 19). Insulin is found also to increase the rate of disappearance of glucose from blood perfused through an isolated limb (Best, 10).

Best, Hoet and Marks (12) showed that in the eviscerated spinal cat insulin causes an increase in the rate of disappearance of the sugar and an increase in glycogen content of the muscles. The glycogen stored accounts for from 40 to 50 per cent of the sugar which had disappeared from the blood. The experiments of Best, Dale, Hoet and Marks (11) show that the sugar which disappears under the action of insulin can be completely accounted for by combustion on the one hand and conversion into glycogen on the other. The effects of insulin in excess represent an intensification of its physiological effects. Lesser holds similar views.

In February of the present year Abel (2) announced that he had prepared insulin in crystalline form. The crystals are rhombohedral and doubly refracting, and have a melting point of 233°C. Slight browning occurs at 215°C. The melting point remains constant on recrystallisation. The crystals give the biuret reaction and the Millon test. The Pauly and ninhydrin reactions are also positive. The pure insulin is very sensitive to alkali. Tested on animals, amounts as small as 1/100 of a milligram per kilo lower the blood sugar to about the convulsive level, 0.045 per cent.

This work has not, so far as I am aware, been confirmed by other investigators.

3. Pituitary. Reference has already been made (p. 312) to the work of Evans and Long on the growth-stimulating effect of the preparations made from the anterior lobe of the pituitary body. Some further details may suitably be given in the present section.

The experiments of Evans and Long were carried out on rats. The animals were treated intra-peritoneally with the finely ground fresh anterior lobe of the ox pituitary, with the result that a veritable gigantism was induced. In one case, in which the experiment was continued for 333 days, the rat which was injected weighed 596 grams, while the control weighed only 248 grams. The increase in weight was partly due to the storage of fat, but the bones were larger and heavier, and the

same applies to the internal organs. It may be recalled that in tadpoles and amblystoma larvae it had been reported that injection of anterior lobe substance caused considerable hastening of growth and metamorphosis.

These results accord with the clinical evidence that the anterior lobe has to do with growth, and especially with the growth of bone. But the effect on the reproductive system is, as Evans and Long point out, a surprising one. Oestrus was suppressed, but the ovaries were large and contained a large number of corpora lutea. The uterus, on the contrary, weighed only half as much as in the controls. There was abundant lutein tissue about the ovum in unruptured, normal follicles, and in atretic follicles. So that the effect of the anterior lobe substance had been to stimulate lutein cell transformation.

A great deal of work has recently been carried out on the various pharmacodynamical actions of preparations made from the posterior lobe of the pituitary body. The action which was first observed (by Oliver and Schäfer) is the pressor effect upon the mammal. This is a very prolonged action as compared with that of adrenin, for example, and the pressure often remains permanently raised. The depressor effect described by Schäfer and Vincent after previous administration of pituitary, only occurs in certain circumstances, though there is very frequently an immunity to the pressor action. The depressor effect on a second and subsequent injection only occurs typically in cats under curare and with the use of dried posterior lobe substance (Vincent and Curtis (97a). Sharpey-Schafer and Macdonald (90) have shown that the alcohol extract containing the depressor substance reproduces in all respects the action of histamine.

From the work of Verney (94) and others, the view that the blood contains anti-diuretic substances derived from the pituitary body, has received considerable support.

4. Adrenal bodies. As first pointed out by Moore and Purinton (78) small doses of adrenin may lower the blood pressure instead of raising it. Several observers have found that this effect is only produced under light anesthesia. Macdonald and Schlapp (74) have recently put forward the view that it owes its occurrence entirely to the anesthetic. They report that depressor effects are only obtainable when the blood pressure is fairly high (over 100 mm. Hg) and when an anesthetic is being administered or is still present in the tissues. The fall is marked under ether and urethane, less marked under chloralose if no ether has been given just before. In the high pressure decerebrate cat from which

all traces of ether have been thoroughly ventilated, no such depressor response can be evoked. On ether being supplied to such an animal, the depressor response quickly returns.[9]

The authors point out that if, as Burn and Dale (see p. 295) suggest, adrenalin vaso-dilatation be due to the production in the lungs of minute amounts of a histamine-like substance, that substance can only be supplied when the animal is anesthetised. The blood pressure response to small doses of histamine itself is little affected by the nature or degree of the anesthetic in a cat with high blood pressure.

If these views be accepted, one argument often used against the tonus theory of adrenin activity will have to be abandoned. It is often urged that the minute traces of adrenin which could be poured into the blood under normal conditions would tend not to raise, but to lower the blood pressure. According to Macdonald and Schlapp, even the smallest possible amount would help to keep the pressure up.

5. Parathyroids. For an account of Collip's work on the parathyroid, see p. 305.

K. AUTACOID SUBSTANCES IN RELATION TO BIOLOGICAL PROBLEMS. Considerable discussion has arisen on the subject of the relation between old age and the failure of endocrine factors. Goodpasture in 1918 (45) gave a full report on the changes in senescence in dogs. A discussion of this paper is given by Hoskins (62), who concludes "that on the whole the evidence now available does not permit any very definite conclusions as to what extent endocrine factors play a causal rôle in senescence."

In regard to endocrine factors which may determine individual characters and personality, much has been written and most of this is of a highly speculative character (see 8).

The doctrine of endocrinology has also been applied to such problems as evolution, heredity and morphogenesis. It is conceivable for example that quantitative variations in the functions of the pituitary body, if they occurred as racial characteristics, and if it could be assumed that they were of a kind which could be transmitted from one generation to another, might result in the production of giant or dwarf types. Sir Arthur Keith, in a very interesting article (66), says that "rightly conceived, Darwin's theory of Pan-genesis is very much of the same char-

[9] Curtis and myself have been able fully to confirm the observations of Macdonald and Schlapp and to add the additional information that the "dip" in the splanchnic rise of blood-pressure does not occur in the absence of an anaesthetic such as ether, urethane or chloralose. ("Lancet," Feb. 12, 1927.)

acter as the modern theory of hormones." Bolk (15) also has treated of the part played by the endocrine glands in the evolution of man. This writer insists that "the whole endocrine system is an organic unit, it is a sort of controlling super-organization in our somatic organism, an *imperium in imperio.*" (See however, p. 308 et ff.) In reviewing this subject Hoskins points out that there is no theoretical necessity for any such assumption as that made by Keith and Bolk. Whether autacoid determinants are actually concerned in the development of racial characteristics must be left to the future to disclose. Careful study is necessary, in the various races, of the endocrine organs from infancy to early postpuberal life, determining both their relative weights and relative degree of activity, and particularly determining whether endocrine activity precedes or accompanies the appearance of the characteristics ascribed to it (Hoskins, 62).

Cunningham (27) believes that there are two distinct kinds of character in all organisms, namely, those of somatogenic origin and those of gametogenic origin. Somatic modifications by means of autacoid substances affect the determinants in the gametes. His theory supposes that every part of the body gives off special substances which have a special effect on the corresponding parts of the chromosomes. He even suggests that bones of different parts of the body give off different autacoids. In discussing the development of the antlers of the stag it is suggested that an exostosis formed on the frontal bone as a result of repeated mechanical stimulation, due to the butting of stags, gives off an increased quantity of intermediate waste products of the same kind as the tissues from which it arose gave off before. These products act as an autacoid on the gametocytes, stimulating the factors which in the next generation would control the development of the frontal bone. It will be seen that the author makes two assumptions: 1, that all products of metabolism may act as autacoid substances, and 2, that acquired characters may be inherited. The first of these has been dealt with on page 288 et ff. The second could not appropriately be discussed in this place.

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THE PHYSIOLOGICAL EFFECTS OF TROPICAL CLIMATE

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The idea that living bodies receive modifying impressions as regards form and qualities from the physical environment is of ancient origin. For example, Hippocrates was aware of the potency of "air, water and places" in moulding human types and in determining their behavior. The coöperation of the environment in creating the variety of manifestations of animal life will, however, remain an hypothesis until binding experimental proof is forthcoming. Such a proof should of course not be limited to the morphological phase alone but should also include the modifiability of functional levels by altered physical factors. At the present time Climatic Physiology, being a recent acquisition by science, is not prepared to answer satisfactorily such theoretical questions raised by the evolutionary Biology. Its development, especially the special branch thereof in which we are primarily interested in this paper, has been mainly dictated by practical motives as regards the health and welfare of individuals or races who have taken up their abode in a new climatic environment.

The term climate was used by medical writers in the eighteenth century for expressing "l'ensemble de toutes les circonstances naturelles et physiques au milieu desquelles nous vivons dans chaque lieu" (Cabanis). The etymological derivation of the term justified this wide definition which in more or less changed wording has been retained by several more recent medical writers. The progress of science has, however, divested climate of its accessory attributes and provided for each of them a separate experimental approach as regards medical and biological inquiries. In the majority of such considerations "medical" climate has become synonymous with "physical" climate: the sum of all the meteorological phenomena which characterize the average state of the atmosphere at any locality of the earth (Hann). Hand in hand with this more precise definition of climate has gone the emphasis of the atmospheric conditions as constituting the essential agency by which the geographical environment acts on the living organism.

The new straightforward conception of climate has imposed upon the investigator the duty of safeguarding the climatic interpretation of any findings by strict observance of the homogeneity of the material from other angles. Such ideal experimental conditions can only rarely be produced in natural climates. It is more than probable that some of the conflicting results which have been reported by physiologists in such climates may find their explanation from difficulties of controlling the material used. Because of the same handicap it has been proposed to supplement any experimental undertaking of this sort in its natural field by properly controlled animal experiments in artificially produced environments. "The ideal procedure in work along these lines is a coöperation of anthropological observation and animal experiment."

But even if we define climate in its more circumscript sense it will appear illogical to speak of the direct physiological effect of a certain climate. Any physiological effect discovered is evidently not attributable to the climate as an entity but rather to the meteorological elements, pressure, temperature, humidity, light, etc., which compose it. The suitability of a climate for physiological studies must largely depend on its homogeneity as regards the meteorological factor on which attention is focused and which is the most prominent for the characterization of the climate concerned. For this reason, altitude climate has proven so eminently useful for studies in which the barometric pressure is the deciding factor.

For investigations on the effect of temperature and allied meteorological factors one is dependent in field work on the climates which may be summarized as "latitude climates." With regard to these, the prospects for finding usable conditions for biological experimentation are often frustrated by the heterogeneity of weather conditions which exist in many localities. For example, in cold and temperate latitudes the weather becomes a more outstanding feature than the climate itself. Not so in the tropics. "Das Wetter ist hier zugleich das Klima." For the greater part of the year the climate becomes a succession of equal combinations of meteorological elements the annual range of which seldom exceeds the diurnal range. Even in regions bordering on the semi-tropics where the seasons commence to make themselves felt one possesses ample opportunity to carry on investigations under ideal conditions. Because of this equality of the tropical climate it is destined to become utilized in an increasing degree for studies relating to the modifiability of external characters and physiological functions of animal life by the group of physical factors which enter into relationship

with the body by either augmenting or abstracting its energy. It should be remembered, however, that the equality of the tropical climate by itself may constitute a separate meteorological factor to be reckoned with in tropical adaptation. Very little is known to what extent life processes are dependent in their proper functioning on fluctuations in weather conditions but every day experience supports the assumption that such fluctuations are beneficial. If this is true, the monotony of the tropical climate deserves attention. "There is far too much climate and far too little weather in the tropics."

The direct effect of a tropical climate as an entity may be expressed in one word: acclimatization, individual or racial. The latter may be assumed to be complete in native races living in the tropics and considerable attention has been given to comparative studies of the physiological functions of the colored races as compared with the white type of man. It must be recognized, however, that the variance in nutritional and other living habits will render such comparisons of doubtful value. A racial acclimatization has also developed in such communities of white descendants which for centuries have inhabited tropical regions. The question whether, to quote Jousset's belief: "l'action du milieu exterieur tend a assimiler le colon aux indigènes du pays qu'il vient habiter" or whether he preserves the characteristics of his ancestry, are problems for the solving of which information has been sought in such white settlements. Reference to such attempts may be found elsewhere (7, 59, 83, 145); it suffices here to say that in no case do these settlements fulfill the requirement of consisting of pure descendants of immigrated whites. And even if this were the case the continuous exposure to the ravages of tropical diseases has probably rendered them useless for climatic physiological investigations.

If we desire to gauge the racial acclimatization we are therefore compelled either to await the outcome of such unique experiments in racial adaptation which, for example, is going on on a grand scale in Tropical Australia or else to seek analogies by breeding suitable animals under natural or artificial tropical conditions for many generations. Meanwhile our knowledge of tropical adaptation will be limited to the individual phase of acclimatization with addition of one or two descendant generations. Generalizing, we may distinguish three periods as regard the effect of the tropical climate on the individual: 1, the immediate response; 2, the adjustment and stimulation period; 3, the attainment of equilibrium. It has been deemed unnecessary in this review to include references to studies of the first group, since they have received

adequate attention in previous papers of this journal in connection with the effect of short exposures to heat and light (40) and also with the reviews on the heat (9) and water (123, 146) regulation.

It has been pointed out that utilitarian aims pervade most of the investigations which have been published in this field. It is well nigh impossible to review the gathered material without discussing to some extent the practical applications which have been debated. For example, if we succeed in demonstrating beyond a doubt the existence of physiological deviations from standards in tropical man, we are led to inquire whether some of these deviations imply a harmful effect. If this be the case, the desirability presents itself of neutralizing such effects by modifying artificially the climatic factors which may be responsible for the change. It will be remembered, however, that with regard to these practical issues opinions have been expressed by men with tropical experience, which opinions, if substantiated, will deduct materially from the practical importance of physiological work in the tropics. According to some of these statements the only obstacle to the settlement of tropical regions by the white man lies in the easily remedied prevalence there of diseases of exogenous origin (35, 73, 147). In other quarters (120) the nutritional issue has been stressed as exceeding the climatic one in its significance for the welfare of the tropical resident. Great caution must at any rate be exercised in proclaiming the harmful effects of physiological abnormalities. Biological qualities of tropical residents even if they differ from those elsewhere, may be quite "normal." Another question is whether they are compatible with the same degree of physical and mental efficiency.

HISTORICAL. In a general way the historical development of Tropical Physiology may be divided into three periods. The first era commenced with the inauguration of a colonial policy by the European nations. The conviction that the immigrants were affected by the vicissitudes of the tropical climate and needed special precautions to counteract these vicissitudes is plainly visible in some of the tropical medical treatises from those olden days (86, 112). Lind wrote: "Men who thus exchange their native for a distant climate may be considered as affected in a manner somewhat analogous to plants removed into a foreign soil where the utmost care and attention are required to keep them in health and to inure them to their new situation, since thus transplanted some change must happen in the constitution of both." From mere inspection many correct deductions were drawn by these pioneers which were embodied by Johnson, the English colonial physician, in his remarkable

book, *Influence of tropical climates on European constitution* (87) printed in many editions in the early part of the last century. Johnson concluded that "for the power of climatic accommodation man is more indebted to the ingenuity of his mind than to the pliability of his body." One can easily guess that this treatise gave the impetus to subsequent attempts to study in a more qualitative way the effects on physiological manifestations. The work of Davy (49) in 1839 on the body temperature in the tropics may be considered as the beginning of the epoch in which easily procurable data as regarding body temperature, pulse and respiration rate, spirometry, etc., were considered, by a number of English and French scientists sufficient for judging the effects of a tropical climate. The publication in 1885 by Jousset of the book, *Acclimatement et acclimatation* (90) may be taken as the culmination and ending of the second period. "L'organisme se modifie donc dans sa constitution ou dans son fonctionnement" (Jousset). One year later Virchow (182), in an address on acclimatization, laid down some of the principles which have guided subsequent investigators in this field. Virchow suggested: "dass eine solche tropische Anpassung mit materiellen Veränderungen verbunden sei, dass es nicht etwa blos um eine Art Umkostümierung handelt, die äusserlich vollzogen sei, sondern dass eine innere Umwandlung, zum Teil ganz neue Organverhältnisse geschaffen werden müssen." It can be historically verified that this speech of Virchow stimulated the voluminous production in tropical Physiology and Biochemistry which since that time has emanated from the Dutch Indies. The interest in such work spread gradually to the Philippines where medical officers of the American army and men of the Bureau of Science made valuable contributions, and to Australia where the "white policy" has favored any work which might throw light on the chances of white settlement in the tropics. Sporadic contributions have since then also been published elsewhere in the tropics. As a special characteristic of this third epoch we may mention the increasing emphasis on the biochemical phase and on the value of animal research to supplement human observations.

MEDICAL METEOROLOGY OF THE TROPICS. A handicap which will considerably delay a survey of tropical climate for the special purpose of the physiologist results from the fact that the latter is furnished by the physical meteorologist only with the mere rudiments of usable data and that he therefore will be compelled to gather his own material to better suit his purpose. In drawing his demarcation lines for the tropical zone the physical climatologist has exclusively made use of dry

bulb temperature data and enclosed the climatic region in which we are interested within the +20°C. isotherms (Supan), inside which zone an equatorial belt has been portioned off for which the average temperature of the coldest month is 20°C. While for plant geographical considerations such a scheme proves satisfactory, it is inadequate, for obvious reasons, for animal physiological surveys, since the comfort of man and other higher animals is determined by humidity and wind as well as by temperature, these three factors together controlling the cooling power. Continuous observations of the wet bulb temperature which Haldane and others have shown to be a far better indicator of body comfort than the dry bulb temperature exist for very few places within the tropics and data on wind velocity are still more scarce. Griffith Taylor (178) has meanwhile proposed a scheme by which he claims to show in a graphical way the relative suitability of selected climates for human habitation. His "climographs" are constructed by plotting for each month the average wet bulb temperature against relative humidity. Leonard Hill's katathermometer, which must be recognised as the most convenient instrument for reading off directly the dry and wet cooling power available in a place has not yet been given the extensive application to tropical conditions which it deserves. Besides the few data for subtropical regions which have been published by Hill (81) the only systematic material on the cooling power in the tropics so far as I am aware has been gathered by Buxton (27) in Samoa. In this locality the average dry kata at 9 a.m. was 3.2 for February and rose to 4.3 for July, at noon the minimum 3.0 was found in December and the maximum 4.6 in July, at 3 p.m. the range of monthly averages was 3.5 to 5.0. The means of wet kata readings for the same times of observation: 13.5 to 18.3, 12.9 to 19.4 and 13.0 to 20.0. These figures do not show any extreme reduction in cooling power but the continuous exposure even to such moderate cooling power reductions is probably an important factor to be reckoned with. Moreover, they apparently represent out-of-door conditions at open places and in general the available cooling power in the tropics must probably be rated considerably lower. This applies especially to in-door conditions, for which some suggestive data have been published from Tropical Australia (174). The prospects to arrive at any reliable expressions for the amount of cooling power at the disposal of tropical residents will always be disturbed by the insistence of man to interfere with natural conditions by means of housing and clothing. Nevertheless it is highly desirable for the physiological survey of the tropical climate

to develop means by which it will be possible to obtain in as many places as practical continuous records for the cooling power and to calculate, for instance, the total annual loss of heat from surfaces maintained at the same temperature as the human skin. Such comparative data will evidently go further than any isotherms or climographs in defining and classifying tropical climate in physiological terms. They will undoubtedly demonstrate a wide range of tropical climates with regard to their physiological favorability as measured by cooling power. In this paper we expect to deal chiefly with that kind of tropical climate which is found in coastal regions.

There is a great need for a systematic survey of light conditions in the tropics. The black bulb measurements which have been tried in a few places are open to serious objections and can hardly be given any credence as conveying any idea regarding the degree of insolation effect on the human body. Knipping (94) has proposed an elaborate technic by which quantitative measurements may be obtained of the energy impingement for different parts of the spectrum. It can hardly be expected that such a method which requires specialized training could be given the extensive use which is desired. The same objection applies to the pyrrheliometric method. It is regrettable that the studies of tropical light which were carried on by Freer (61, 62) and collaborators in the Philippines were discontinued. It appears that their technic better than any others would fill the requirements for more universal adoption. The photocatalytic reaction induced when oxalic acid in presence of uranyl salt is exposed to light is simple enough, it has been thoroughly standardized and since the effective rays do not extend above 530 $\mu\mu$ it comprises the physiologically most interesting region of the spectrum. Moreover, a considerable amount of material has already been collected not only for the Philippines but for other tropical countries as well. The average per cent of oxalic acid decomposed in one hour was for Manila 12.5, for the Philippine highlands 14.2, for Honolulu 13.8, for Kuala Lumpur in Malaya 15.3, for Khartoum 17.6, for Townsville, Australia 17.5 (176). Similar series in Washington, D. C. gave in the average 11.0 for summer and 10.0 for the winter months. At many occasions figures were, however, registered in the latter place which corresponded to conditions as they prevail in the tropics.

Effect of light. It has been consistently claimed by some writers (121, 187, 188) that the physiological response of an organism to the tropical climate is altogether due to the exposure to light of shorter wave lengths and that the protection offered by the more or less de-

veloped skin pigment is directly correlated to the more or less successful acclimatization to a tropical environment. Anyone who scans the evidence adduced will become sceptical about these conclusions. The propounders of the hypothesis have failed to recognize that the physiological effect may be due to other factors as well. The sweeping conclusions drawn by Woodruff (187, 188) working in the Philippines, as regards the greater handicap suffered by blondes in the tropics appear to have been conclusively refuted by Chamberlain (34) and others in the same place. The suggestion by Woodruff that orange red underwear might prove beneficial was given an extensive trial with negative results (134). It has been pointed out that tropical animals seldom expose themselves to the sun. With regard to native races the same thing holds, and regarding white settlers it is a common experience that such individuals who shut themselves up in houses are even more affected than others whose habits bring them frequently out into the open (174).

The animal experiments of Aron (6) and Shaklee (148) seem to prove that any ill effects from insolation in the tropics are due to the absorption mainly of longer rays and to a resulting failure of the heat regulation, and that when measures are taken to facilitate the heat loss, for example by fanning, body injury is prevented. While, however, Aron was led to deny any increase in the resistance of monkeys to solar exposure, Shaklee noted that such an adaptation may occur due to increased perspiration from the sweat glands which the latter investigator proved existed in certain parts of the body of the monkey. No information is available regarding the power of tropical sunlight to penetrate into deeper tissues and into the blood. The demonstration of methemoglobin in organisms which had been exposed to the tropical sun may indicate such an effect (64). On the other hand, reports from competent sources (155) seem to minimize the effectivity of tropical sunlight insofar as direct photodynamic action is concerned. It will be reserved for animal experiments under well controlled laboratory conditions to test the specific effect of light of the same intensity and composition as it occurs in the tropics in order to evaluate the participation of this physical agency in the supposed deterioration of the white race in the tropics. The technical difficulties to be overcome have prevented such undertakings. From the scant biological evidence available, from the fact that the spectrum extends in the tropics to the same wavelength as in the temperate climate and from the relatively small increase in photodynamic action as measured in vitro it may be anticipated that,

at least for higher mammalians, tropical light in its physiological application may not transgress the borderline where the stimulating action ceases and the deleterious action begins. But it seems possible that this very stimulating action by itself is undesirable and that the sunlight—the longer rays by their direct heat effect, the shorter ones by being converted into heat—adds a considerable burden to the heat dissipating mechanisms which are already overtaxed. In experiments on small animals it was found that the growth which already was retarded from humid heat alone suffered a still greater reduction when the radiation from strong electric globes was added to the environment (168). And similar experiments under the stress imposed by high temperature and high humidity in diffuse light have repeatedly yielded, with regard to physiological effect on animals, results which compare well with the results of human experimentation in the tropics. The trend in newer contributions to tropical physiology seems to be to minimize the action of the "actinic" light and to focus attention on the existence in tropical regions of a continuous reduction of cooling power, which, moreover, unlike direct insolation, is omnipresent and requires more elaborate means of counteracting. One becomes inclined to reduce the importance of insolation in tropical physiological considerations and to consider it as a special case in connection with the etiology of sunstroke. That, indeed, exposure to intense light is capable of producing a localized hyperthermia of the central nervous organs has been borne out by investigations of Hill and his co-workers (82).

Body temperature. If it be true that the physiological response to a tropical climate is primarily due to the cooling power factor, the acclimatization process to such a climate should in the first hand consist of means to adjust the heat regulatory mechanism to the highest attainable degree of efficiency in order to preserve a normal body temperature. It is a curious fact that in spite of the numerous attempts to assay this heat-regulating efficiency by body temperature measurements this simple point should still remain one of the most contested points in the whole field of tropical physiology. Mention has already been made of the pioneer work of Davy (49, 50) nearly a hundred years ago. Davy measured the mouth temperature of several of his fellow passengers in two visits to the tropics and found this temperature to be in average 0.5°C. higher in the tropics than in the cooler climates. In a similar series but in more recent times Neuhauss (131) taking the rectal temperature, also registered a positive difference in favor of the tropics but the change was very small. Others (90, 143) have noted a more

pronounced increase especially during the first weeks of the tropical sojourn and cases are on record where the tropical elevation of body temperature was altogether missed (18, 63, 177, 184). The average of 3000 mouth temperature readings on soldiers in the Philippines (34) likewise agree with accepted standards for cooler climates. Attempts made to compare the body temperature of native races with that of Europeans in the tropics have generally yielded negligible differences (55, 90). Young (189), while working with white inhabitants of the tropics, has employed unusual care and concludes that the rectal temperature is the only reliable one in the tropics and that, while the resting body temperature in tropical residents correponds to figures encountered in cooler latitudes, the rise after muscular exercise may be considerable, which latter point was confirmed by Young in collaboration with Breinl and others (194). Breinl (21) found in white stevedores working in tropical heat rises up to 101.7°C. although many rectal temperatures were recorded which might have been found at a similar heavy work in cooler climates. Davy demonstrated somewhat higher body temperature in the hotter season in the tropics than at times when the weather was less trying.

Since attempts to arrive at definite conclusions by the employment of human material have stranded on the difficulty of deciding on reliable base lines for comparison, it becomes necessary to consider the better controlled animal series under artificially produced tropical conditions. For example, in rats (175) living in four environments graded as to their cooling power, (dry kata 1 to 7 and wet kata 4 to 19) a progressive rise in rectal temperature was demonstrated with the lowering in cooling power, the difference for the extreme environments amounting to approximately 1°C. Analogous results have been reported elsewhere (77, 165) for small animals in environments in which only the external temperature was regulated. These facts in conjunction with the individually controlled human experiences in the tropics lend support to the idea that the body temperature may remain slightly elevated and that, therefore, the heat regulating mechanism may fall somewhat short of complete adjustment at least in more severe hot environments.

Skin temperature. A small rise in the body temperature may not necessarily imply a harmful effect; on the contrary, it may even be advantageous by increasing the gradient for conductive heat loss. For determining this gradient the skin temperature is, however, more decisive than the body temperature. It seems obvious that the flushing of the skin in a tropical environment raises the skin temperature.

Experimentally, Jousset (90) by a naturally crude technic found the skin "hotter all over the body." By the thermocouple method Aron (6) measured skin temperatures in the Philippines. In the shade the greater part of the body showed skin temperatures between 32.5 and 33.5°C. In the sun the human skin rose to about 36°. If the sun exposure was continued the temperature of the skin dropped when perspiration broke out. Malays, while theoretically absorbing more heat from the sun, showed a less maximal skin temperature rise than whites because an earlier sweat secretion took place. Gibbs (64), however, found that darker colors maintain higher maxima than the lighter. In animals which lack sweat glands both skin and subcutaneous tissues exhibited, when exposed for a long time to the sun, temperatures above those compatible with life.

PARTITION OF HEAT LOSS IN THE TROPICS. The possibility suggested itself to early investigators that racially acclimated organisms in the tropics might have acquired the facility of getting rid of excess heat by radiation and conduction at a more rapid rate than individuals in cooler climates. The skin pigment was thought to play a rôle in accelerating heat dissipation by non-evaporative means. Woodruff's (187, 188) suggestion that the pigmented skin radiates heat quicker than the white skin has been experimentally refuted by Eijkman and Hill (81). Glogner's conclusions, drawn from some rather crude arm calorimetric experiments (66, 67), that the skin of a native loses heat by convection more rapidly than the skin of a white man, were not supported by the experiments of Eijkman (55) on living subjects. Neither did Eijkman find any difference when he used excised pieces of skin for comparative calorimetric experiments. It appears that very little can be gained by employment of such methods for solving problems which can almost a priori be disposed of on theoretical premises. Of greater interest is that part of Eijkman's contribution which is concerned with the part played by perspiration in heat loss. He found that Europeans in Java gave off in average 16 per cent more heat by evaporation than the natives. A corresponding decrease of 14 per cent of heat loss by conduction took place in the whites. Eijkman explains this difference as resulting from an exaggeration of the evaporative heat loss in the latter. Only by having his Malay subjects drink large quantities of water could he bring up the perspiration to the same levels as in the Europeans. By dividing the white subjects in groups according to body weight Eijkman was able to show that the amount of perspiration decreased at a more rapid rate than the body weight. For the group weighing in

average 63.5 kgm. the perspiration amounted to 228 grams for the experimental period, while for the 54.9 kgm. body weight group the perspiration totalled 172 grams or practically the same as for natives with the same body weight. These results strongly suggest that the favored position enjoyed by the natives with regard to the relatively large portion of heat loss which is removed by the less exhausting channel of conduction may be due to their smaller bodies. In this connection it may be mentioned that in experiments on mice in artificial tropics (169) it was found that on exposures to excessive temperatures larger animals succumbed more quickly than smaller ones, due probably to an exorbitant water elimination.

The importance of an efficient perspiration in the tropics has led several investigators to compare the number of sweat glands per skin area unit in white immigrants and in natives. The results are conflicting. Eijkman (58) found in the former an average of 162 and in latter 160 glands per square centimeter. On the other hand Clark (39), in the Philippines, showed that Malays possess 12 to 15 per cent and Negritos 27 per cent more sweat glands than Europeans. It seems, however, that such comparisons are of doubtful value since it has been shown that the quantitative outpour of sweat is less important than its distribution on the skin to form an even film. Suggestions have been made that the chemical properties of the sweat may in some way affect its physical behavior (87, 132). The available information regarding the chemical composition of sweat in the tropics is limited to some analyses of nitrogen (53, 54, 191) and chlorides (84, 180) which all show normal levels, and to a few pH estimations (174).

Heat loss and skin area. Considerations have been given the problem whether an animal transferred to a hot environment may possess a mechanism to facilitate heat loss by such modifications of its body build which result in a larger skin area. Experiments to prove this point are difficult to carry out on human subjects. The generally weedier body shape of native races and the tendency of immigrated whites to become thin may indicate that such a mechanism may also operate in man in spite of the fact that he is because of his sweat glands better situated than most other animals. Anthropological measurements of natives in the tropics have indicated that the extremities tend to become longer (179). As regards smaller animals data have been presented to show that such body modifications as referred to may be important. In mice exposed to artificial tropics the skin area available for each gram of body weight was for males 4.26 and for females 4.21

square centimeters as compared with 3.78 in control males and 3.80 in control females (169). Besides the tails became longer, the ears larger and the scrota pendulous and hairless. In more recent work on rats (175), the rôle for instance of an enlarged scrotum in assisting in heat loss has been proven almost beyond doubt. The relative tail length has been shown to be inversely proportional to the cooling power (138, 139, 164, 166, 169, 175). The ratio of body length to body weight tends also to be dependent on the cooling power in the same manner.

Mass of metabolizing protoplasm. Some relief in preventing overheating might ensue if the organism were able to reduce the total mass of living tissue. The reduction of adult body weight in the tropics has been mentioned and will again be discussed in connection with growth. The weight of the liver and the spleen is less in negroes than in the white race (14, 15). Besides the smaller body weight rats exhibited in humid heat (175) an average reduction of 20 per cent in the relative weight of certain internal organs such as the liver, spleen, kidneys and testes, but when the cooling power was enhanced by fanning or when the air was less humid, the decrease in the relative weight of the body organs was less pronounced. Also in real tropics it has been shown (173, 174) that the assistance to heat loss which resulted from fanning was instrumental in raising the relative weight of body organs far above the levels for the controls. In the first mentioned rat series the reduction of the relative thyroid weight was especially significant, the "muggies" in proportion to the total body mass possessing slightly more than half of the thyroid mass as the controls. The improving effect of "wind" and lowered humidity were also here sharply defined.

Basal metabolism. It is obvious that a body, the heat regulation of which is laboring under the stress of tropical conditions, would be eminently benefitted if it were endowed with a mechanism of "banking its fires." Earlier writers assumed (132) without proof that such is the case. The observation of Mayer (125) in 1840 that the venous blood in the tropics is redder than in a cooler climate (noticed also by other pioneers in the field (49)), an observation which was destined to lead Mayer to the discovery of the first law of thermodynamics, was assumed by him to signify a lowering of the oxidative level of the body in the tropics, an interpretation, however, which was built on faulty premises. The first real experimental work, viz., that of Eijkman (56) in the nineties, seemed to conclusively prove that the basal metabolic rate in the tropics occupies the same levels as in temperate climate. His data

recalculated in a more recent polemic paper (57) to suit modern terms indicate a basal rate of 40 Cal. per square meter an hour for adult men, which agrees with accepted standards. When de Almeida, 20 years later, published his discovery that in fact a reduction of 20 per cent may take place in the metabolic rate of both white (1) and colored (2) inhabitants of the tropics, his announcement was received with incredulity and his technic was questioned by Eijkman and others. Shortly before the appearance of de Almeida's papers a series of respiratory metabolic experiments were published by Young (192) in Australia, which were planned to discover any correlation between resting metabolism and cooling power, but because the post-absorptive state was not observed in the subjects the results fail to fulfill the conditions demanded of strict basal rate observations. Young did not succeed in his main purpose, but thought that his data were indicative of a rise in the metabolism in hot environment.

The wide divergency in the results of the three aforementioned investigators, representing all possibilities, viz., 1, no change; 2, decrease; 3, increase, does not, however, imply that any of them has been guilty of gross technical errors, but it simply emphasizes the complexity of the problem. The writer believes that the second viewpoint has much in its favor and that even the others when properly understood may lend support in the same direction. It should be stated, however, "that the multifarious combinations of climatic factors which compose the tropical climate and the enhancement of the variability which accompanies adaptation to any new environment do not militate against an occasional basal metabolic level in healthy individuals in the tropics that equals or even surpasses the standard levels established in a temperate climate." It will be remembered, for instance, that Knipping (91) found evidence of an initial rise in the basal rate which was followed later by subnormal values. It should also be borne in mind that special precautions should be observed in the tropics if as close an approximation as possible to the real basal metabolism is desired. The ideal time for conducting such experiments appears to be that part of the year when the oppressive heat gives way to somewhat more comfortable climatic conditions. The success of de Almeida to discover the lowered basal rate may be partly due to this circumstance. By employing a different experimental technic the same writer has recently confirmed his own results (3). Whilst in his first series the range was rather large—whites: 25.7 to 37.6 Cal., average 30.6 Cal.; Negroes: 26.3 to 37.2 Cal., average 32.9 Cal.—in his last series the range narrowed

down to 32.3 to 34.6 Cal. Sundstroem (174), working in Tropical Australia, has arrived at conclusions which completely support de Almeida's results. In male subjects the range for the basal metabolism reduced to the surface unit was 25.5 to 36.1 Cal., average 31 Cal. and for female subjects 22.1 to 33.8 Cal., average 27.8 Cal. Montoro (129) in Cuba found for men 30.9 to 39.1 Cal. and for women 28.2 to 36.8 Cal. Fleming (60) demonstrated a decrease in basal rate in Filipinos. Recent studies of the basal rate in a subtropical climate (New Orleans) have also indicated a diminution (80).

In connection with experiments on the adaptation of rats (175) to climatic enviroments adjusted so as to give a gradient from relatively high to very low cooling power we have tested the relationship of the basal metabolism to a more or less efficient heat loss. It must be borne in mind, however, that in this and other respects it cannot be taken for granted that the acclimatization to a hot climate always proceeds on strictly similar lines in man and in small rodents. It should also be remembered that advantages in procuring controls may be partly neutralized by difficulties in collecting experiments in such lively animals which fulfill the requirements of real basal metabolic estimations. The data have, however, accumulated in fair numbers under an increasing rigidity of procedure, that at least the writer feels tolerably assured that they prove the point that energy metabolism at rest is decreased in hot environments. Not only has the expected drop in metabolic rate occurred in the "muggy" rats, but in environments in which the cooling power in the hot room was raised by continuous fanning the basal metabolism was elevated to a point midway between the control and "humid heat, stagnant air" environment. Calculated under the assumption of 9.1 as the factor in the surface area formula for rats the averages of one "immigrant" series were: controls 41.5 Cal., "wind" rats 36.6 Cal., "muggies" 32.3 Cal. In another similar series the corresponding figures were: 41.5, 36.5 and 33.4. For a third series, in which the hot room rats were born in the hot environment the same figures were 40.2, 37.2 and 31.8. It was also ascertained that the diminution in relative oxygen consumption did not become manifest before the principal growth period had passed. Furthermore, it appeared to be of interest to test the physiological behavior of rats which were maintained at the same oxidative levels as the controls by injections of thyroid extract. The results of this latter part of the study have strongly suggested, for instance by their lowered resistance to still higher temperatures, that the tampering with the adaptive change as

regards a low basal rate is harmful to the animals. Although any local infection never occurred, the body temperature tended to remain abnormally high. Indications were also procured to show that forced exercise every other day led to higher basal levels without any concomitant harmful effects, which observation is interesting in connection with the claim that exercise is beneficial to tropical man. The absence of exercise in other rat series explains the results of an experiment in which the caloric intake was utilized as an indicator of the levels of the energy exchange. These levels were nearly the same as the basal levels and the gradient of the metabolism for the rat series again followed the cooling power gradient.

Tentative experiments by Knipping (91) have indicated a lowering of the specific dynamic action in the tropics as compared with figures obtained in the temperate climate. On the other hand a few observations of the rise in respiratory metabolism caused by injections of alanin in "heat" rats (175) have not suggested any change from normal. Of considerable interest as regards body comfort of man doing physical work in the tropics is the question of muscular efficiency under such conditions. Eijkman (58) has referred to some unfinished work of his which did not show any change from standard figures.

It cannot be denied that the theoretical deductions as regards the value of a low basal rate in combating overheating are minimized when it is considered that, for instance, a man living a normally active life in the tropics is benefitted by such an adaptation mechanism only when he is resting. When he is working the total energy level is of such a height that the relief obtained becomes almost negligible even if the standard metabolism remained the same as at rest. Evidently the basal rate level is affected by the raised body temperature. All the investigators (5, 32, 54, 72, 142, 174) who have studied the food consumption of tropical residents, who were allowed to follow their usual habits as to diet and exercise, have failed to discover any diminution from standard figures.

Blood distribution. The hyperactivity of the skin which results from the forced physical heat regulation makes continuous demands for an increased blood supply up to 50 times the normal. The immediate result, if the total blood volume were constant, would necessarily be an impoverishment of the amount of blood directed towards the central organs. Exact information is lacking regarding the relative distribution of the blood at any time of a tropical sojourn. Such an inequality of the relative blood supply has, however, been proclaimed

by Osborne (133) as being the only firmly demonstrated physiological effect of the tropical climate. It appears, however, on the basis of investigations by Barcroft and his collaborators, that the body may be able quite soon after arrival in the tropical climate to readjust affairs, at least partly, by augmenting the total blood volume. So far as I am aware, the only observations which might serve as a circumstantial evidence towards indicating how much the central organs may suffer in their blood supply from the plethora of the peripheral capillary bed have been made by Rattray (143, 144) and Jousset (90). The former took repeated spirometric readings for a number of fellow passengers throughout a sea voyage. An increase of the vital capacity, amounting to in average 12 per cent, took place after reaching the tropics and persisted for several months in tropical waters. Rattray suggested that the increased air content of the lungs was due to a lessened blood content of these organs. Jousset confirmed on a large material Rattray's results, but found that as a rule a readjustment took place in a few months, the vital capacity often dropping below the initial figures. Jousset also doubted the explanation given by Rattray and suggested instead that a lowered oxygen tension was to blame. He reports, however, figures which show that the weight of excised lungs is consistently less in the tropics than elsewhere.

More precise information is required before we are able to lay stress on the consequences which the redistribution of the blood, which thus has been indicated, may have with regard to a proper functioning of vital parts of the body. Possibly they are correlated with the retardation of growth both of the body at large and of internal organs. Possibly they have something to do with the "hypo" level of the basal metabolism, if this is not determined by subactivity of the thyroid, by modifications of the permeability of cellular membranes or by an innate reduction of the oxygen consumption of tissues of tropical animals which could be demonstrated "in vitro." One careful experiment which the writer has obtained for a "tropical" rat suggests that the third alternative does not hold. On the other hand, the hyperemia of peripheral parts may account for the stimulation in growth which we have found occurs in some of these parts of the body in a hot environment.

WATER REGULATION. It has been repeatedly stated in the literature that a disturbance in the water regulation which results from profuse perspiration cannot fail to be of physiological importance. The experimental work is quite conflicting. This is natural when it is considered that the chapter of the distribution of water still remains one

of the most obscure in the science of physiology. Any method by which it is hoped to throw light on the water regulation in a tropical climate, or elsewhere, necessitates such a combination of various analytical procedures that its employment becomes impractical. On the other hand, observations limited to only a single phase are inadequate for this purpose. One may only say that in a hot environment the heat and the water regulations are intimately connected and that an insufficient heat regulation by non-evaporative means shifts the burden and risk of breakdown over on the water regulation. One also feels confident that important phases of tropical adaptation will become intelligible when the question of water regulation will be cleared up.

The "thinness" of the blood which was assumed by early writers (180) to be the rule in the tropics was not confirmed by the Dutch investigators who approached the problem by the specific gravity method (52, 68, 74, 107). Young and his collaborators (194) even believe they have demonstrated a slight concentration of the tropical blood by weighing of total solids and by the refractometric method. A later worker in the Australian laboratory (174) came to the same conclusion in his experiments on humans. He also claims that the blood chlorides exhibit a noticeable retention in a hot environment. He suggested, however, that the concentration was mainly limited to the plasma whilst data obtained by the hematocrit method, by estimations of the corpuscular volumes and by erythrocyte measurements indicated that the formed blood elements actually became richer in water. By analogy the same writer was led to believe that the peculiar behavior of the red cells as regards their water content is shared by other body cells and the phenomenon was interpreted as due to a protective mechanism intended to prevent the desiccation of living matter in consequence of the drain on the water resources to which the profuse perspiration may lead and about which state of affairs the thirst centers for various reasons may not be sufficiently well informed. Some circumstantial evidence was adduced to make it probable that an altered membrane permeability (an increase in the resistance of red cells to hypotonic saline solutions was indicated) and a shift in the lecithin: cholesterol ratio were in some way connected with this obscure mechanism. How close this hypothesis may come to realities will for a long time be difficult to ascertain. Further experiment on these lines on "tropical" rats (175) have, however, indicated that, indeed, there is a tendency of the cells with progressing adaptation, to become even richer in water than those of controls and this seems again to be correlated

with a shift in the lecithin:cholesterol ratio. The only discord between the human and the rat series has been, however, the failure of the plasma in the tropical rat series to become more concentrated. On the contrary, to judge from specific gravity and "solids" estimations, it appears that a dilution of the plasma persists in the rats. Not considering the technical difficulties encountered in the employment of such small animals for such delicate analyses, it is possible than an essential difference may exist between man and the rat as regards plasma concentration as affected by hot environment. Barbour (10, 11, 12) has conclusively shown that a hemodilution takes place in man prior to and accompanying the outbreak of sweat in a hot and humid environment. While his experiments have not been extended long enough to have a direct bearing on the state of affairs which prevails in a tropical climate, the figures rather support the idea that in man the plasma dilution gives way to an opposite condition of this fluid. Of considerable interest in connection with this discussion is his conclusion that the water of the red cells is drawn upon in large amount to supply the water for perspiration. It is possible that in rats the evaporative heat loss does not at any time reach such proportions that in these animals the plasma becomes concentrated.

URINARY EXCRETION. The abundance of the perspiratory flow is reflected upon the water available for excretion by other channels especially by the kidneys. Numerous quantitative data are available (55, 90, 131, 143, 174, 184, 191) to show the reduction of the urinary volume of man in the tropics. It seems conceivable that this phenomenon, when it becomes stationary, cannot fail to interfere with the proper excretion of waste products. It has also been suggested that the permanently high concentration of urine which results may in the long run be injurious to the kidney epithelium and it has, indeed, been assumed by some writers that physiological factors may predispose to a greater prevalence of nephritis in the tropics. On the other hand, Jousset (90) thinks that nephritis is less prevalent in the tropics than in cooler latitudes. It has been suggested (174) that the higher concentration of the tropical urine may involve toxic products which otherwise may be innocuous but by mass action may injure the kidney epithelium. Young (191) found albumen in the urine of a surprisingly large number of otherwise normal individuals in the tropics. Another investigator from the Townsville laboratory (174) claims to have shown a retention, averaging 25 per cent, of the nitrogenous waste products and also an elevation of the chloride level of the blood. He believes

that these findings indicate a lack of water for excretion. The explanation will probably not go unchallenged, since others, on small material, have published tropical data which suggest a normal non-protein nitrogen content of the blood. It is true that rats exposed to low cooling power (175) as a rule also exhibit a high non-protein nitrogen content, but in similar rats the daily urinary volume agreed closely with that of the controls. This throws some doubt on the hypothesis that the disturbance in water regulation in tropical climate leads to retention phenomena.

The composition of the urine in the tropics has been investigated by several workers who agree that with the exception of the high concentration it corresponds fairly well with accepted standards. The lower urea and chloride content which was already pointed out by Jousset and has been confirmed by others results from the partial excretion of these substances in the sweat (111, 191). The nitrogen partition has in man been found to conform with standards (29, 42, 190). In tropical rats (175), however, there was a decided increase of the non-urea fraction. This was partly due to the increase in the creatinin excretion which was inversely proportional to the drop in cooling power. In man the creatinin output has generally been normal but a case of a tropical resident is on record (174) in which the urinary creatinin rose quite markedly without any other cause but climatic being discovered. The reports on the excretion of neutral sulphur are conflicting and do not prove an augmented katabolism of body protein in tropical man. An increase in the ammonia excretion in tropical man has been postulated by Campbell (30) as constituting a physiological effect of the climate and has been interpreted by him as indicating an acidosis. Another investigator (174), while agreeing on the main issue, disagrees as to its explanation. The latter found that the pH of tropical urine fell within the same limits as in cooler latitudes.

In many instances deductions have been drawn in tropical laboratories (19, 28, 29, 51, 191) from urinary analysis alone which should be reserved for complete balance experiments. The only experiment in the tropics of this kind (174) covering, however, only one week and including a man, a woman and a nine-year-old girl, was conducted in tropical Australia at the hottest part of the year. Complete data were collected with respect to water, protein and mineral metabolism and to acid-base equilibrium. The most interesting points in this work were the appreciable retention of nitrogen and phosphorus in the child and a retention of basic elements in excess of acid ones in the same

subject. The adult subjects exhibited an almost complete acid-base equilibrium.

ACID-BASE EQUILIBRIUM. It has been proposed that lack of water of excretion in the tropics may also contribute to producing an alkalotic blood condition. This idea is contrary to the earlier assumption (30), built on fragmentary evidence, that if anything an acidotic state is the rule. An alkalosis was actually found to exist in a fair number of cases examined in tropical Queensland (174) but the universality of this tropical effect still remains to be tested on greater numbers in other types of tropical climate and by direct estimation of the pH. In the Australian work the conclusions were drawn from simultaneously conducted estimations of the alveolar carbon dioxide tension and the alkaline reserve from which the pH was calculated. The alveolar CO_2 tension underwent a diminution which result agrees with reports of Young and his co-workers (194). The alkaline reserve was either unchanged or increased. In one individual on which a considerable number of alveolar air analyses were made the CO_2 tension was lowest in the cooler season and a slight rise took place during the more trying months, but this rise in the "free" CO_2 was overcompensated by a still greater rise in the "bound" CO_2 of the blood. While some doubts may be entertained regarding the validity of these observations as proving tropical alkalosis, more binding appear to be the data which were obtained by use of the indirect method of Barcroft. A "pleionexy" was demonstrated to exist in several inhabitants of the tropics and especially in such persons who were known to be physically less active. The alkalosis which these data seem to prove was removed by work and it is probable that the beneficial effect of physical exercise which is known to anyone with tropical experience may to some extent be due to the shift in the pH. Some scanty evidence is also available to indicate that copious water drinking may in the tropics shift the pH back to more normal levels. Rat experiments conducted in artificial environments with low cooling power (175) support the idea of a tropical alkalosis. By the use of Hastings' colorimetric method it was found that 30 of a total of 39 adapted hot room rats exhibited a pH above 7.40, the maximum being 7.80. Of 18 control rats only 6 fell in the higher pH category, the maximum being 7.45. But on the other hand, if the existence of a tropical alkalosis is confirmed by others, who can guarantee whether it may not be, for instance for man in the tropics, just as normal as a slightly lower pH is for the inhabitant of cooler latitudes?

BLOOD SUGAR. More data are available with respect to the blood

sugar level in the tropics than to any other part of blood chemistry. McCay (118) discovered high fasting sugar levels in Hindus and attributed this to the high carbohydrate content in the diet. On the other hand van Langen (103, 104, 106) claimed to have demonstrated an exceptionally high sugar content in the blood of healthy white inhabitants of the Dutch Indies and blamed the climate for this abnormality. He concluded that diabetics should be warned not to immigrate to the tropics. In the light of the subsequent investigations (16, 43, 60, 140, 154, 174, 193) in this line which were stimulated by van Langen's pronouncement it has become increasingly evident that some technical imperfection must have vitiated his results. A scrutiny of these later investigations makes it clear that not only does the blood sugar level in the tropics never reach an excessive height but it rather tends to occupy low levels. A drop in the blood sugar seems even to occur with a prolonged tropical sojourn and descendants as a rule exhibit lower levels than immigrants. Rat experiments (175) have indicated that a certain parallelism is evident in the decrease in blood sugar and in the reduction of cooling power.

Non-protein nitrogen. In connection with urinary excretion reference has already been made to the conflicting data (16, 60, 102, 140, 156, 174) which are available as regards the total non-protein nitrogen of the blood. Of these the Australian series is the most complete, including not only a "statistical" part but also repeated observations on one individual in the tropics and in cooler climate. Whilst the non-protein nitrogen outside the tropics and also during the cooler part of the year in the hot climate conformed to normal standards a progressive rise in these blood constituents up to 50 mgm. took place in the more trying season. As a rule the total rise in non-protein nitrogen was equally distributed on its various components. On the other hand rat experiments (175) have suggested that low cooling power may cause an increase in the urea and amino acid fractions, but a decrease in the total creatinin, uric acid and nucleotide nitrogen. A small decrease in the uric acid in man has also been shown in Java (16).

Phosphorus of the blood. Sundstroem (174) lays stress on the diminution of the phosphorus of the blood which he found both in white residents and rats in the Queensland tropics and afterwards in rats exposed to low cooling power in artificial climates. He believes that this decrease in the blood phosphorus, acid-soluble as well as lipoid, constitutes one of the more important effects of the tropical climate. No evidence for a reduction in the inorganic phosphorus was, however,

produced. Sundstroem believes that a "hypolecithinemia" is beneficial by assisting in maintaining a low lecithin : cholesterol ratio, which already has been discussed. Still more problematical is naturally the hypothesis that the phosphorus impoverishment may interfere with the synthesis of nuclear material, although some circumstantial evidence was adduced by Sundstroem for this theory by demonstrating a close correlation between the lipoid phosphorus levels and the nuclear morphology of the polynuclear leucocytes and also by showing that the lipoid phosphorus level was extremely low in children at the time of their slowest growth. Subsequent rat experiments have shown a parallelism between the curves of phosphorus content, both acid-soluble and lipoid, of the blood and the curves for the cooling power in four environments which were graded as to this meteorological factor. A few phosphorus analyses of human blood have been published from Java (16). The figures are fairly high, which might be due to seasonal influences, the importance of which has been emphasized by Sundstroem.

Lipoid constituents of the blood. Van Langen noticed in his chemical studies of the blood of Malay subjects (100) subnormal values for cholesterol and believed that these findings indicated a climatic effect but modified his opinion in a later publication (101) in which he emphasized the coöperation of nutritional factors. The blood "fat" was found by the same observer (108) to be as a rule decreased in the tropics. In chemical blood studies on white inhabitants of tropical Queensland (174) the cholesterol usually conformed with accepted standards, although some figures were registered for the hottest part of the year which were decidedly high. In a "seasonally" conducted series proof was obtained for an antagonistic behavior of the lecithin and cholesterol curves, high levels of the former coinciding with low levels of the latter and conversely; which again seems to support the idea that some mechanism may be operating in the hot environment which aims rather at the adjustment of the ratio between the two lipoid substances than of the absolute level of any of them. Radsma (140) working in Java has recently published some cholesterol analyses of the blood of whites and Malays. The results closely resemble as to ranges and averages the figures from tropical Australia which have been discussed. There does not seem to be any difference between the blood cholesterol levels in the two races in Java.

Suspension stability of red cells. In connection with the blood chemical work (174) which was carried on in North Queensland attention

was directed to the possible value of changes in the suspension stability of red cells in gauging tropical adaptation. A decrease was as a rule observed in this property of blood suspensions and correlations were suggested with other acclimatization phenomena. Continued experiments in this line on rats (175) exposed to low cooling power have confirmed the results of the human experiments. The figures representing the height (in millimeters) of the clear plasma layer after 30 minutes standing of the micro containers at an angle of 45° and at 37°C. are: control rats 8.2, "native muggies" 10.5, fanned heat rats 10.9, "muggies" 13.8, recent heat immigrants 15.4. These figures suggest that length of heat exposure and the severity of the climate may be determining factors. Besides the work has quite strongly indicated that the suspension stability is correlated with the difference between the specific gravity of the plasma and the corpuscles, which circumstance establishes the value of this novel test in tropical physiological investigations in which we have reason to believe the water regulation is one of the most important phases.

NUMBER OF RED CORPUSCLES. All early writers on the effect of a hot environment on man believed in the existence of a tropical anemia with a climatic etiology. The sallowness of the skin, which is usual in tropical residents, was given as a symptom of such an anemia and some pioneer blood countings (2.4 to 2.8 million reds, Magelhaes in Rio, ref. Jousset) seemed to point in the same direction. If the technic was beyond reproach the cases must have been pathological. The advent of more acurate microscopical methods led several investigators in the Dutch Indies (52, 69, 70, 149) to undertake studies of the red count and the hemoglobin content of the blood. All of these studies yielded the surprising result that man in the tropics with regard to his blood morphology is not worse off than man in cooler climates. Work of a similar nature was carried out in the Philippines where Wickline (185) however, while finding a small increase of the red count, showed a drop in the color index. The still more abundant material of Chamberlain (36) on American soldiers confirmed these results as also did the series of Cuthbert (45) in tropical Africa. Breinl and Priestley (22) found no striking abnormalities in healthy school children in tropical Queensland as regards the number of erythrocytes and color index. A number of explanations have been advanced to account for the sallowness of the skin of tropical residents which prevails in spite of the normal red count (163).

In more recent investigations it has been pointed out that far from

interfering with the function of the erythropoiëtic organs the tropical climate may often act to stimulate these organs. Such an effect was already indicated, however, by the blood studies of Maréstang (122). This new viewpoint is especially supported by some individually conducted investigations (174, 184). In hot desert climates an increase of the red cells has also been found (151, 186). Of great significance in connection with this problem is the finding by Barcroft (13) of an increase in the number of reticulated red corpuscles in a hot environment. Knipping (91) noted on a sea voyage an appreciable increase in the blood hemoglobin of several of his fellow passengers. He also carried out blood regeneration tests on dogs after pyrodin injections. The hemoglobin content returned to normal in a shorter time in the tropical experiments than in the control ones. In two cases of severe hemorrhages, Eijkman found in Java a normal time for the blood regeneration. Mice exposed to humid heat have exhibited a red count which in average was 10 per cent higher than in the controls (172). Hemoconcentration was in this case thought to be a contributing factor, but subsequent findings of a hemodilution in small rodents under such climatic conditions may suggest that the blood-forming organs of the heat mice were more active than those of the controls.

White blood corpuscles. Regarding the number of white cells found in the blood of tropical inhabitants the published data indicate either normal (34, 99) or, in quite a number of cases, subnormal (152) figures. The occasional finding of higher white counts (22) may be indicative of a failure of sufficient control of the material as regards intestinal and other parasites. More individually conducted investigations (174) have generally shown subnormal white counts which after the return to a cooler climate have come back to normal levels. Mice exposed to a humid hot artificial climate likewise showed a definite leucopenia (172). The differential count has been investigated in several tropical laboratories (22, 34, 99, 109, 174) and as a rule the polynuclears have been found reduced.

A considerable interest has become manifested in the behavior of the polymorphonuclear leucocytes as classified according to Arneth. A shift to the left of the Arneth index was discovered by Chamberlain and Vedder (37) in healthy Filipinos and was assumed by them to signify a physiological effect of the tropical climate and also a lowered resistance to infections in native races. White soldiers in the Philippines showed the same effect to a less degree. Breinl and Priestley (23) found the same change in the Arneth count in healthy white children in tropical

Queensland and stressed its physiological nature but questioned its connection with the resistance to disease. Breinl has also shown the same characteristic of the nuclear picture in Australian (25) and New Guinea aboriginals (24). Failures to confirm this interesting finding with respect to the morphology of the leucocytes have been reported from other tropical places (99, 115, 124) but on the other hand series are on record (174) which make it probable that such negative findings might have been due to seasonal remissions in the blood picture and that the phenomenon in question may be correlated with chemical blood changes which occur in tropical residents.

Pulse rate. The observations which in great numbers have been reported on the pulse rate as affected by tropical climate (21, 35, 50, 90, 131, 184, 194) lack the standardization for instance with regard to psychic factors and exercise which could render them of value in a system of adaptive mechanisms. It would be interesting to correlate the pulse rate with the basal metabolism—a rise in the first part and a drop at more advanced acclimatization, if our information is correct—and a corresponding curve in the pulse rate has indeed occasionally been demonstrated. Evidently the circulatory disturbances which result from the filling of the peripheral capillary bed tend to obscure the correlation of the pulse with the metabolic rate.

Blood pressure. Jousset (90) gives in his book a considerable number of pulse tracings obtained both from natives and from whites in various stages of tropical adaptation. As time went on a change took place in the type of the tracings, the initial low amplitude being replaced with wide oscillations and a marked dicrotism. The conclusion of Jousset that this means a change from a lowered blood pressure in the beginning to normal or even higher pressure at further advanced acclimatization has been confirmed in a direct way by some more recent observers. Of special value are those sphygmomanometric studies in which the base line has been obtained before the subjects entered the tropics (91). On the other hand other reports (21, 35, 89) deny any tropical effect on the blood pressure and still others believe in a protracted lowering influence on this physiological manifestation (41, 130). Violent exercise in hot environment leads to a rapid rise in systolic blood pressure followed by a drop (194) and in laborers the blood pressure curve tends to reach lower levels in the later part of a hot day. Systolic and diastolic curves run parallel (21).

Respiration rate and volume. It is difficult to coördinate the studies in this line since a diminution has been reported almost as

frequently as an augmentation. Rattray (143) found in the tropics a decrease of 7.6 per cent (as compared with England) in the rate and volume of respiration. Jousset (90) found an increase in the rate of in average 2.4 per minute; the increase was reduced for a prolonged tropical sojourn but not to the normal level. Jousset was aware of the value of a stimulated respiration in promoting an enhanced water evaporation. On a large number of white soldiers Chamberlain (34) showed an average respiration rate of 19.3 in the tropics as compared with 17 to 18 in America. Again Wick (184) believes in a decrease. Knipping's series (91) is probably the most valuable of them all. He found a decrease of the rate of up to 37 per cent, but an increase of the volume up to 41 per cent. Knipping calculated that in average 248 Calories were gotten rid of by the excess water elimination in consequence of the augmented respiratory volume. The lowered alveolar CO_2 tension which seems to be the rule in the tropical climate also points in the direction of an increased respiratory volume.

Growth. No comprehensive evaluation of the effect of the tropical climate on growth is yet possible but a few ideas have been conveyed by the investigations on the subject. Rattray (144) found that naval cadets on several cruises in tropical waters grew in height more rapidly than in England but that their growth in weight was retarded. Rattray considered the resulting weedy body shape an unfavorable climatic effect. Investigations in Java (88) also indicated a more rapid growth in stature than in weight. Any tendency to a weedy body form was not observed in white children in tropical Queensland which might have been due to a somewhat less trying climate. We have already referred to the theory that a weedy body shape may be beneficial to the heat regulation.

Statistical growth series in tropical Australia (174) have not borne out the unfavorability of the environment by a consideration of the variability in growth, an increase of which according to Robertson tends to accompany conditions which are inimical to physical development. The same tropical growth experiments have demonstrated that humid heat may under certain conditions act as a stimulant on the adolescent growth of white children. The growth curves for both stature and weight occupied for the periods 9 to 14 years higher levels than for children of the same racial stock in temperate climate. This stimulation in growth coincided with the hottest part of the year and if we can trust the tentative experiments which were carried out to test the biochemical composition of the blood of these children at the time

of the year when the growth stimulation waned we are led to question the favorability of the rapid adolescent growth and whether it is compatible with a harmonious development in all directions.

Only by use of animal experiments under artificially produced conditions may one succeed in studying separately the growth effects of each of the meteorological factors, temperature, humidity, wind and light. Such experiments are available for mice (168) and rats (175). From these experiments it appears that the humid heat constitutes a growth retarding factor, especially in animals which in already growing state are introduced into the hot room. In mice which were born in the "tropical" room a temporary growth stimulation was shown to occur. Succeeding generations may behave differently and after a couple of generations with extremely stunted growth a generation was again reared which exhibited a more satisfactory growth. Strong light which alone was shown to possess a growth stimulating effect, when combined with humid heat suppressed the growth below the levels exhibited by the series exposed to only humid heat. Of singular interest is the improvement which follows motion of the hot and humid air by use of electric fans. Already indicated by mice work, this phenomenon has been firmly established in two separate subsequent series on rats. It can therefore be stated with tolerable confidence that any measure which is employed to raise the cooling power in a humid and hot environment will at least partly neutralize the growth retarding effect of the tropical climate. It even appears that a definite proportionality exists between the growth velocity and the available cooling power.

Reproduction. For obvious reasons it is difficult to procure reliable data on this part of the physiology as applied to man in a tropical climate. The insufficient data (71, 174) we possess with respect to the first incidence of menstruation of white girls indicate that it does not take place exceptionally early. As is well known, native girls menstruate very early but the proof that the climate alone is responsible is by no means easy to produce. Steinach and Kammerer (158) believe that a moderately severe tropical climate will lower the age of maturity, whilst on the other hand extreme conditions may work the other way. In the tropical obstetrical literature it has been stated, for example, that the hot climate predisposes to sterility of women, to menstrual abnormalities, to abortions and to post-puerperal hemorrhages (33, 116). The menopause is assumed to occur earlier (90). Again, animal experiments under natural or artificially produced tropical conditions are destined to contribute materially to our knowledge of

reproduction in a hot environment. Some experiments (79, 160) have been reported on the histological structure of testes and ovaries as affected by high temperature, which studies indeed have demonstrated profound abnormalities, but the drastic environmental conditions usually employed deduct considerably from their value for the problem here under debate. Steinach and Kammerer, whose procedures seem to have been less inimical to the general welfare of their rats, report that the fertility of the females and the size of their litters were both affected in direction of a diminution. Elsewhere no change in the size of the litters of "tropical" mice has been found (168). Przibram (137) has published some data on the oestrous cycle of rats exposed to high temperature, which data he believes show no effect.

Under the expert supervision of Prof. H. M. Evans, work has been for the last year carried out in this laboratory (in collaboration with the Department of Anatomy) to study the reproductive functions of rats as affected by reduced cooling power. Previously it had been found that male rats which had been exposed to humid heat and stagnant air conditions for six months, beginning at the age of four weeks, exhibited a condition of the testes which was indicative of sterility. Litter brothers which were continuously fanned possessed normal testes. According to the new set of experiments by a standardized technic the onset of sterility was delayed. In seven months old hot room males we succeeded in obtaining positive matings of every rat with oestrous females from outside, although the willingness to mate seemed to be less pronounced than in the controls. Each of these positive matings resulted in a normal pregnancy. When the same males were 15 months old they were again repeatedly mated with oestrous females, but at this time, while sperm was found for the majority of the males, the females nevertheless failed to conceive with the exception of four experiments in which the employed males were born in the hot room. The controls were sexually normal. The conclusion seems therefore warranted that such reductions of cooling power which may also prevail in actual tropics may in certain cases ultimately lead to a sterility of the males due to inactive sperm. With regard to the females it was found that the vagina opened as a rule in the hot room animals at an earlier age than in the controls and especially so in those females which were not fanned. Extensive data have been collected as regards the oestrous cycles which in the hot room females have been found to resemble closely those of the controls. Pronounced abnormalities have been noticed only at times when the cooling power was further reduced. When the atmos-

pheric conditions have again become stationary the cycles have returned to a normal type. In the majority of cases the hot room females have been successfully mated with one of the potent "muggy, native" males but the pregnancies have only in two instances proceeded to full term and resulted in the birth of living young. Mostly the fetuses have died. Typical resorptions have been proven to take place, whilst attempts of other females to expel the dead fetuses have led to fatal uterine hemorrhages.[1]

Growth of hair and nails. Since the fur of animals becomes an impediment to the heat regulation in a hot environment a thinning of the coat has been suspected as constituting an adaptation mechanism to lowered cooling power. Darwin cites several instances of the fleece of sheep being affected by great heat. Comparative weighings of the shaved off hair covering of experimental animals (164, 166, 170) have led to contradictory results. On the other hand observations have been reported (170) which show that mice which for several generations have been reared in a hot room may give rise to an almost hairless modification, which again when suddenly exposed to a cool environment acquired a fur within a very short time. The explanation which is nearest at hand, namely, that the skin itself might have been directly stimulated, seems to be the less probable alternative, the other alternative that the loss of hair and subsequent growth might have been correlated with variations in the general anabolic level receiving support from some experiments on human hair growth which are on record (174). In this latter research series the growth of the hair of a man was ascertained for some time in the tropical climate and subsequently at cooler latitudes. It may be assumed that the hair on the head of man has lost its rôle as a heat insulator. Nevertheless, it was found that the hair grew in the tropics at a rate which was in average 11 per cent slower than in the temperate climate. Furthermore, the most rapid rate coincided in the tropics with the first part of the oppressive season, when also other functions were improved, whilst a sudden decline in hair growth occurred when metabolic processes showed signs of slowing down. Moreover, return to a cooler climate resulted in a considerable stimulation of hair growth, which growth then proceeded with seasonally determined cycles, exhibiting a maximum in June and a minimum in December. The total nail growth was in the tropics retarded by 11 per cent,

[1] From more recent mating experiments on "tropical" rats in this laboratory it appears that the reproductive function of these animals may considerably improve already in the second "descendant" generation.

equally as for hair growth and also the seasonal fluctuations were in their main parts identical with those of the growth of the hair.

PIGMENTATION. The integumental parts of the body deserve attention from another angle in tropical physiology. The pigmentation has been repeatedly given prominence in such work, but because of the extremely incomplete information regarding the biochemical reactions which underlie formation of pigment very little headway has been made in the application of this problem to tropical work. The deepening of the skin pigment in hot climates has been accepted as due to solar radiation and its purpose to protect against this same radiation, a circuitous way of reasoning which, however, seems to satisfy most writers on the subject. The effectivity of sunlight in producing pigmentation in unprotected areas of white skin and the apparent immunity of such pigmented patches to irritation are well known facts. In experiments on recessive albino mice (170) it was found that strong light was capable of producing a creamy colored modification and microscopical examination of the hairs showed fine golden yellow granules identical as to size and location to granules seen in more recent rat experiments in black or grey hairs which had been bleached by the hot environment. The most peculiar circumstance, however, was the discovery that such yellow mice strains also originated in the hot and humid climate without the agency of strong light. The phenomenon was provisionally interpreted as a real pigmentation brought about by the external heat and therefrom resulting higher skin temperature and the hypothesis was formulated that the optimal temperature for pigment formation might be nearer the tropical temperature than the temperature at which the animals had been previously bred. From some quarters (Sumner, *Ecology*, vol. 6, p. 368) the accuracy of these observations, in so far as they signify the appearance of real pigment in albino animals, has been questioned and the lack of real granules in "tropical" white rats (175) which in great numbers have exhibited the same creamy to reddish yellow color certainly strikes a discordant note. But even if the effect of humid heat in altering the coat color of white rodents would be nullified there remains to be considered the very striking reddening of the fur of black and grey rats which has been observed to occur. The hairs in these cases have lost their black pigment granules which have been replaced by yellow granules in decreasing sizes and occasional hairs have been seen which show gradations from larger to minute yellow granules and to absence of granules with the yellow color pervading the hair shaft. It seems possible that in the

pigment formation the "condensation phase" may fail in some cases to result in visible granules and that such an explanation may be applicable to the lack of granules in the hairs of white rats which have acquired color when exposed to low cooling power. At any rate, we may feel confident that a hot and humid environment affects the pigmentation of animals. It must be left for future investigations to decide the precise nature of this change and the place it will find as a link in the adaptive mechanisms to "tropical" climate. It is possible that the pigment, of the hairs at least, lacks any useful rôle and that it, like the hair growth, only forms visible expressions of the state of general metabolic processes. Two single observations may suggest this. A thyroidectomized black rat reared in a cool environment also showed a reddish tinge of the fur. On the other hand a female "muggy" rat which originally was grey colored but which in the hot room had turned red had a litter and died six weeks later. Examination of the fur exhibited a sharp demarcation line between a distal red and a basal purely grey portion of the hairs. Since in all other "red" rats the color commences from the roots of the hairs it becomes interesting to speculate as to the rôle the disturbances in metabolic functions which took place at the time of pregnancy might have played in affecting the hair pigmentation. One naturally thinks in the first hand of endocrinal organs, adrenals, thyroids or a coöperation of both.

ENDOCRINAL FUNCTIONS. More than once the opinion has been expressed that the glands with an internal secretion may be disturbed in their functions by a tropical climate. Rearing animals in hot environments has by several observers (79, 127, 161) been reported to result in histological appearances of the thyroid which indicate subfunction. In "heat mice" and also in mice exposed to strong light a slight decrease in the resistance to injections of acetonitril has been demonstrated (171). The decrease in size of the thyroid which takes place in rats exposed to reduced cooling power has already been mentioned, but is evidently of little use in a discussion of the thyroid function. The drop in basal metabolism in similar environments may have an indirect bearing on the problem in question (174).

Indications of an exhausting effect on adrenals by a hot environment have been produced (44). That the adrenal cortex may in some way be affected by continuous heat exposure has been suspected but no direct evidence has been offered (174). The adrenals do not seem to participate in the progressive relative weight decrease as shown for thyroids and also for other organs (175). That the function of the

islands of Langerhans may have to be considered is suggested by observations of Voegtlin and Dunn (183) who noted an increased toxicity to insulin doses in consequence of raised temperature of the rooms in which the animals were kept. These writers, themselves, however, believe that absorptive differences may account for the results. Knipping (91) while failing to observe any histological change in the thyroids of swine imported to the tropics, claims to have seen the cellular structure of the hypophysis gland affected in these animals. Steinach and Kammerer (158) observed a proliferation of the interstitial cells of the testes of rats which were reared in a warm environment.

Nervous system. It remains to point out the few attempts which have been made to study the functions of the nervous system in hot climates. Such studies have been undertaken mainly in the hope of throwing some light on the psychological phase of tropical reactions in white colonists. That such reactions actually exist can not be doubted, that the nervous system frequently becomes upset in residents of hot climates is equally true but in such cases it is extremely difficult to make the climate alone responsible for these conditions. At least it appears problematical to be able by physiological and biochemical methods to furnish the desired evidence for altered functions of the nervous system. Possibly the indications of disturbed hydration phenomena may offer a clue. At the present time the available information is of a purely physiological type. Of historical interest only are Jousset's (90) comparative studies of the tactile and visual sense as affected by the tropics. Of course no change was found. Grijns (75) claims to have shown a prolongation of the reaction time to stimuli in consequence of tropical sojourn. Experiments in the same line elsewhere have failed to support this conclusion (174).

The disparity in the observed responses to a tropical climate, which becomes distressingly manifest in a sectional discussion of the field would probably become intelligible if we were enabled, in an individualizing way, to fit each separate functional effect into its proper place in the adaptation process at large. It is conceivable that individuals may not be all alike in their choice of the acclimatization mechanisms which nature has placed at their disposal. Some may succeed in striking the medium road preferring to divide up the burden imposed by a trying environment on several functions without unduly overtaxing any of them. n such cases it may be difficult by our as yet imperfect methods to detect any measurable deviation from accepted standards. On the other hand it appears to be fairly well established that others may ex-

hibit abnormalities as a consequence of their failure to equilibrize the acclimatization process.

Since only in exceptional cases attention has been given to the need of correlation of the findings as regards the physiological effect of tropical climate the time is yet far off when it will be possible to decide whether such a climate predisposes to a different type of functional coördination or not. Van Langen (105) has suggested that the trend in the tropics is towards the development of a sympaticotonic type. The rôle of the endocrinal system in affecting any change in physiological coördination in hot climates may, however, correspond better with modern thought.

There may be some truth in the severe criticism of a writer who characterizes the output in the tropical physiological field as "a number of hypotheses in chaotic disorder without proofs and without a leading idea being manifest in the various considerations." This may partly be due to the fact that no such eminent physiologists have been attracted to this field as for instance to the altitude physiology. The writer has also become increasingly convinced of the futility of trying by individual efforts to find the final answers to the many problems which the tropics offer the physiologist. However, looking back upon the scientific production especially during the last 40 years we encounter in our opinion a considerable number of hints and workable ideas which we believe will prove useful when a new era commences, when "group" studies by competent men will replace individual efforts, when sufficient financial means will be available to consider not only scattered localities but the tropical region as a whole, when it will be possible to follow up any promising phase to a point beyond mere "suggestions" with due consideration of the correlations with other body functions, and when, consequently, the whole science of physiology will be placed in the tropical frame.

This paper is not the proper place for outlining the practical issues which could conveniently be included in such a program. Among problems of a more general physiological interest may be mentioned: 1, the water regulation in connection with the heat regulation; 2, cellular permeability and hydration phenomena; 3, the interaction of endocrinal glands; 4, the muscular efficiency in connection with the lactic acid problem; 5, the blood as a system; 6, growth, reproduction and longevity; 7, morbidity and mortality as affected by physiological changes. The list is chosen at random and is far from complete. Finally, we may say that a single firmly proven qualitative biochemical change will be more valuable in demonstrating a real effect of the tropi-

cal climate than a score of quantitative measurements of altered physiological manifestations.

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ERRATUM

In the January issue, no. 1, volume vii, in the article by Baas-Becking and Parks:

Foot of p. 94. The minimal efficiencies should be 7.5 and 5.9 per cent respectively, instead of 0.6, as given for both experiments.

Table, p. 104, 3rd column, 2nd line, should read 6.7–29.6 (limits) instead of 0.6–29.6 (limits).